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COMMUNICATIONS

ROLE OF OXYGEN IN THE GENESIS OF RETROLENTAL FIBROPLASIA

A PRELIMINARY REPORT

BY

NORMAN ASHTON, BASIL WARD, AND GEOFFREY SERPELL

Department of Pathology, Institute of Ophthalmology, University of London

In view of the present controversy centring in the role of oxygen in the aetiology of retrolental fibroplasia, we have thought it essential to investigate the influence of varying concentrations of oxygen upon the immature retina. Since it is now well established that the earliest stages of this disease are angioblastic in nature and present as an overgrowth of the developing retinal vessels, it was necessary to select a laboratory animal in which the anatomy and embryology of the retinal vessels were comparable with those in man. In the cat, embryo vascular budding commences at the disc between the 35th and 45th day of intra-uterine life, but the vessels do not reach the retinal periphery until about 3 weeks after birth, whereas, in man, the retinal vasculature is complete at birth. The degree of retinal vascularization in the full-term kitten at birth and in the ensuing 3 weeks is therefore comparable in extent to that in the premature baby. Since, with minor variations, the retinal vascular development is in all other respects very similar to that in man, the kitten appeared to be ideal for our purpose.

Our experiments have, therefore, been designed to investigate the immediate and remote effects of high, moderate, and low concentrations of oxygen upon the process of retinal vascularization during the first 3 weeks of the kitten's life. Not all of these experiments have been completed and several others are now in progress, but the findings so far obtained appear to be sufficiently striking and significant to warrant a preliminary communication.

Full experimental details and a discussion of the results will be given in a subsequent paper; this report will be confined to a description of the effect of high concentrations of oxygen upon growing retinal vessels, and the subsequent developments which follow the transfer of the animal to ordinary atmospheric conditions.

Material and Methods

Standard bacteriological incubators were converted to gas chambers into which oxygen was passed through an inlet tube and the flow so adjusted as to provide a concentration of 75–80 per cent. of oxygen at normal ambient pressures. The

oxygen levels were measured with a B.O.C. oxygen analyser at half-hourly intervals throughout the day and night. CO_2 readings were made with a Fry's gas analyser, and temperature and hygrometer readings were taken at hourly intervals.

The mother cat and test kittens were placed on a shelf in the chamber and maintained in the experimental conditions for a period of some days; at the end of each experiment the kittens were anaesthetized and, after one eye had been removed for section, the left ventricle was injected with Indian ink. The remaining injected eye was then removed and placed in fixative for 12 hrs; after freezing, it was opened transversely, and the retina was removed and mounted flat for study under the stereoscopic microscope.

In some of our more recent experiments it has been possible, by using foster mothers, to obtain control animals from the same litter, of the same age, and of similar weight; this is a desirable precaution in view of the variability in development of the kitten's retinal vessels. The results described in this paper, however, are those obtained in high concentrations of oxygen and are far beyond the limits of normal variation.

Experimental Findings

Two typical experiments will be described.

Experiment 1.—Cat and three kittens (K_1, K_2, K_3) 3 days old.

Plan.—Put mother and litter (K_1, K_2, K_3) in incubator maintained at 60–70 per cent. oxygen for 4 days (K_1, K_2) and 6 days (K_3) to demonstrate:

(*a*) Effect of 4 days' hyperoxia at 7 days old (K_1, K_2).
(*b*) Effect of 6 days' hyperoxia at 9 days old (K_3).

Results (both retinae were injected with Indian ink):

(*a*) Only a few vessels were seen around the disc. Maximum outgrowth (MO) 2mm. No other injected vessels apparent in retina. High power microscopical examination showed constricted vessels containing blood. *Tunica vasculosa lentis* and hyaloid artery (TVL and HA) normal. Both eyes from both kittens showed the same picture.

(*b*) Both retinae showed only one or two spicules of injected vessels around the disc. MO 1 mm. No other vessels visible. TVL and HA normal and fully injected.

Conclusion.—This experiment shows that conditions of hyperoxia were able to obliterate developing retinal vessels. In the normal animal of corresponding age the retinal network is dense and the maximum outgrowth over 6 mm. (Figs 1 and 2, opposite). In this experiment, however, there were no controls of the same age and same litter.

Experiment 4.—Cat and six kittens (K_{1-6}) 1 day old. One foster mother.

Plan.—Kill and examine K_1. Put K_2 and K_3 with foster mother in air. Put K_4, K_5, and K_6 with mother in incubator at 75–80 per cent. oxygen for 4 days. Then kill K_2 and K_4, transfer K_6 to foster mother in air for 3 days, and change mother and K_5 to 10–15 per cent. oxygen for 3 days. Then kill K_3, K_6, and K_5 to demonstrate:

(*a*) Normal retina at 1 day (K_1).
(*b*) Normal retina at 5 days (K_2).
(*c*) Normal retina at 8 days (K_3).
(*d*) Effect of 4 days' hyperoxia at 5 days old (K_4).
(*e*) Effect of 4 days' hyperoxia followed by 3 days' air at 8 days old (K_5).
(*f*) Effect of 4 days' hyperoxia followed by 3 days' hypoxia at 8 days old (K_6).

FIG. 1.—Control kitten, 1 day old (Exp. 4, K_1, L). Normal developing retina. There are three vascular complexes, maximum outgrowth 6 mm. Proliferation most dense at periphery. (Compare Fig. 2). Injected Indian ink. Mounted flat. ×7.

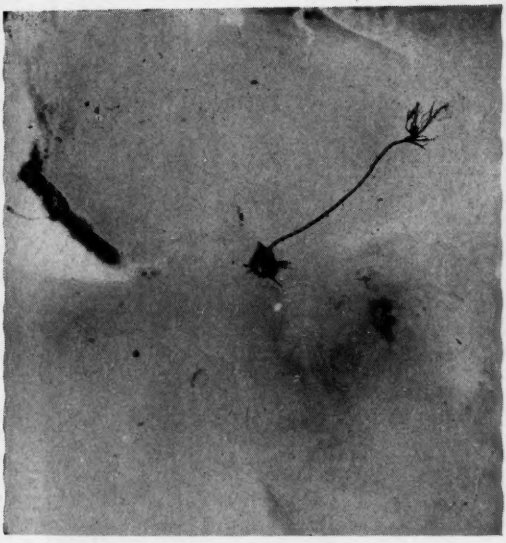


FIG. 2.—Experimental kitten, 9 days old (Exp. 1, K_3, R). Shows effect of 6 days' continuous hyperoxia (60–70 per cent. oxygen). Apart from a few attenuated vessels around the disc, the vascular complexes, which should be even more advanced than those shown in Fig. 1, have been completely obliterated. No other vessels are visible in the retina. Hyaloid artery and tunica vasculosa lentis normal. Injected Indian ink. Mounted flat. ×7.

Results.—In every case one eye was removed for section and the results in the other (injected) eye were as follows:

(*a*) Normal retina showing most dense proliferations at periphery. MO 7 mm. TVL and HA normal.

(*b*) Normal retina showing most dense proliferations midway between disc and periphery. MO 6 mm. TVL and HA normal.

(*c*) Normal retina showing most dense proliferations at periphery. MO 9 mm. Vessels had reached ora on nasal side. TVL and HA normal.

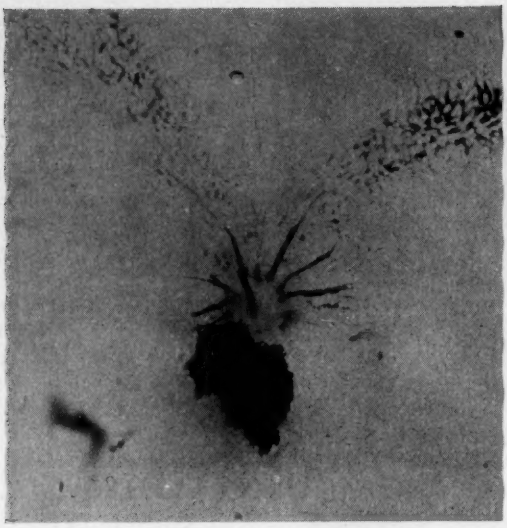


FIG. 3.—Experimental kitten, 5 days old (Exp. 4, K_1, R). Shows effect of 4 days' continuous hyperoxia (75–80 per cent. oxygen). Only nine or ten small spikes of injected vessels remain around the disc. Elsewhere the vascular bed is obliterated and in some areas it contains trapped blood. A portion of the normal hyaloid artery may be seen in the centre of the disc. There is a small leak of Indian ink below the disc. Injected Indian ink. Mounted flat. ×19.

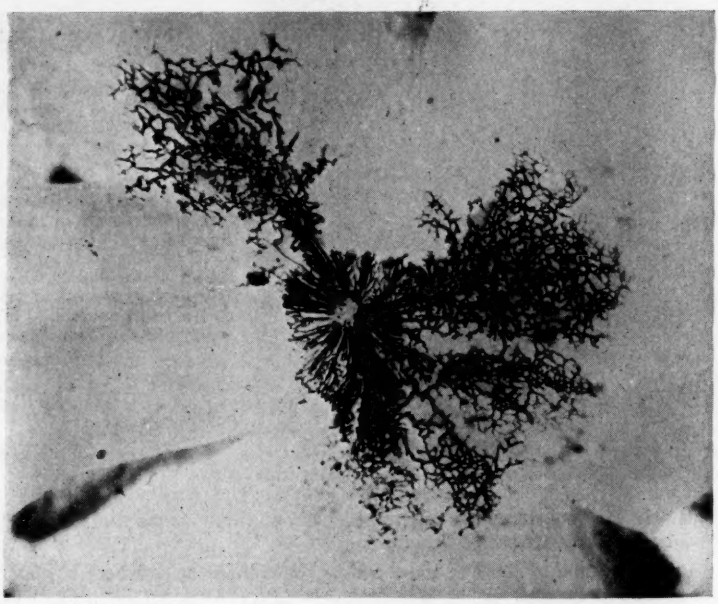


FIG. 4.—Experimental kitten, 8 days old (Exp. 4, K_2, R). Shows effect of 4 days' hyperoxia (75–80 per cent. oxygen) followed by 3 days' air. The pre-existing vascular complexes have partially re-opened but the capillary network is of a grossly abnormal architecture, being cobweb in type without definition of arteries and veins. In the periphery of the retina the vessels tail off into a thrombosed network from which many haemorrhages have occurred. Vascularization appears to have recommenced in the region of the disc, and in this area there is a circular zone 4 mm. in diameter showing a more normal architecture but a richer plexus of vessels. Injected Indian ink. Mounted flat. ×9.

(*d*) Only nine or ten small spikes of injected vessels present around disc. MO (injected) 1 mm. Elsewhere vascular bed obliterated except for islands of thrombosed vessels. No haemorrhages. TVL and HA normal (Fig. 3).

(*e*) Showed roughly three complexes. MO 5 mm., but network irregular and of cobweb type with no differentiation of arteries and veins. No increase in density at periphery where capillaries tailed off into a thrombosed network from which many haemorrhages had occurred. In region of disc vascularization appeared to have recommenced; in this area a circular zone, 4 mm. in diameter, showed a more normal architecture but with a richer plexus of vessels (Figs 4, 5, and 6). TVL and HA normal.

FIG. 5.—Control kitten, 8 days old (Exp. 4, K_8, R). Shows normal architecture of developing vascular bed. Arteries and veins may be distinguished and there is a well marked capillary-free peri-arterial zone (Compare Fig. 6). Injected Indian ink. Mounted flat. ×50.

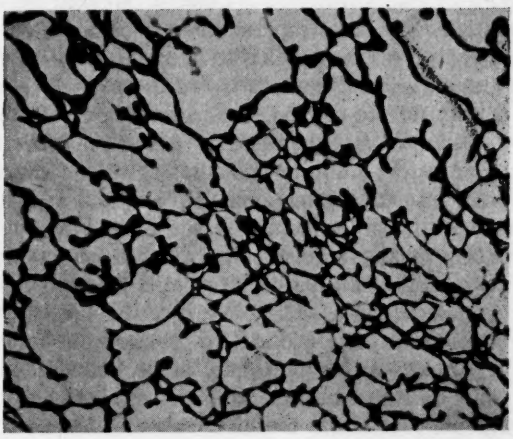


FIG. 6.—Experimental kitten, 8 days old (Exp. 4, K_8, R). Shows effect upon capillary network of 4 days' hyperoxia (75–80 per cent. oxygen) followed by 3 days' air. The transfer to air has led to the re-opening of the capillaries which had been obliterated by the period in oxygen. The network is grossly abnormal, no arteries and veins can be discerned, and the picture resembles that of the histological pattern of pulmonary emphysema (Compare Fig. 5). Injected Indian ink. Mounted flat. ×50.

(*f*) No injected vessels seen except on nasal side where a fine cobweb network of vessels extended 4 mm. from disc. Beyond this point thrombosed capillaries could be seen and there were a few haemorrhages at capillary tips. No evidence of

normal vascular architecture, but vessels around disc obscured by leak of Indian ink. TVL and HA normal.

Conclusions.—This experiment was completely satisfactory in that the degree of retinal development before the test was known and each experimental animal was paired with a control litter-mate of the same age and comparable weight. The findings completely confirm the conclusions reached in Experiment 1—that high concentrations of oxygen are able to obliterate developing retinal vessels—and they further show that some of the collapsed vessels contain trapped coagulated blood (K_4). After transfer to air for 3 days, such vessels as remain patent appear to re-open, giving rise to a grossly abnormal cobweb network of capillaries. The normal architecture is not restored. This re-established blood supply would seem to be inadequate and the process of vascularization recommences from the disc (K_6). Transfer to hypoxia instead of air did not appear to make any difference and the greater growth of vessels that might have been expected did not occur. The area of the disc, however, was obscured in this case by a leak of ink.

General Conclusions

The findings from our experiments, of which two examples are quoted above in this preliminary communication, indicate that high concentrations of oxygen (60–80 per cent.) at atmospheric pressure are able to obliterate the ingrowing vessels in the developing retina of the kitten. Since the tunica vasculosa lentis, hyaloid artery, and other vessels examined in the body showed no structural alteration, and the fully mature retina of the kitten was not affected in this way, it would appear that this process represents a specific effect upon growing vessels or a fundamental interference with the process of vascularization. In the latter respect it is possible, for instance, that conditions of hyperoxia extend the nutritional range of the choroid to include the inner layers of the retina, so that the developing retinal vessels lose their growth stimulus, become redundant, and atrophy. The well known vasoconstrictive effect of oxygen may also play a part in this process. Further experiments, to be reported later, have shown that the extent of vascular obliteration induced by oxygen is directly proportional to the degree of immaturity of the retinal vascularization, to the duration of exposure to oxygen, and to the degree of the oxygen concentrations.

Obliteration of the vascular channels is irreversible in many vessels and this appears to be due to some extent to the coagulation of entrapped blood. After transferring the animal to air, such vessels as remain patent refill with blood, but the resulting vascular architecture is grossly abnormal, consisting of an irregular cobweb of vessels without definition into arteries or veins, and extensive haemorrhages may appear at the periphery of the re-opened network. The picture of the injected vessels resembles that of the histological pattern of an emphysematous lung. This re-established blood supply appears to be totally inadequate for the requirements of the retina when the animal is breathing air, and vessel growth into the ischaemic retina recommences from the disc region.

At the present time we do not know the ultimate outcome of this severe interference with the development of the retinal vasculature, but our most recent experiments have shown new vessels growing into the vitreous 18

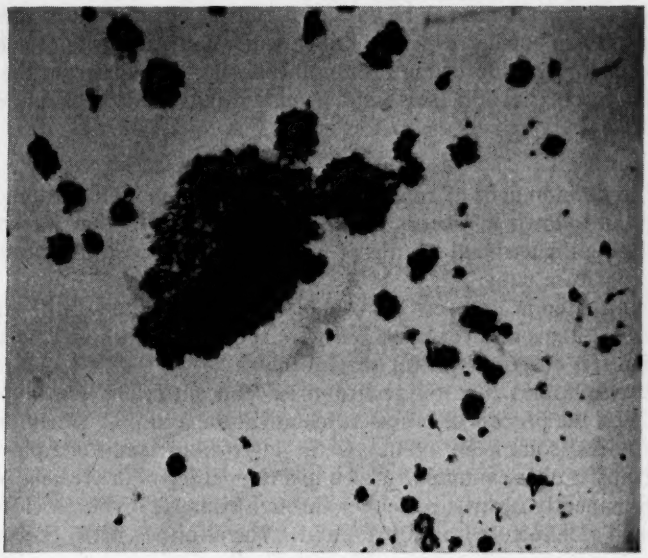


FIG. 7.—Experimental kitten. The animal was subjected to 5 days' hyperoxia (75-80 per cent. oxygen) followed by 18 days in air. Vitreous removed from surface of revascularizing retina shows glomerules of blood vessels and proliferating endothelial buds extending into it. Injected Indian ink. ×27.

days after exposure to high concentrations of oxygen (Fig. 7), and this was accompanied by retinal detachment 30 days after such exposure. It is clear, therefore, that high ambient concentrations of oxygen can destroy the normal process of vascularization in the retina of the kitten, resulting in abnormal vascular proliferation and retinal detachment when the animal is subsequently transferred to air.

Since the development of the retinal vessels in the kitten is so closely comparable to that in man, it is probably justifiable to draw analogies between our experiments and the conditions to which the premature baby is subjected in the nursery incubator. Indeed, we feel that it is highly probable that a similar obliteration or vasoconstriction of the retinal vessels may occur in the premature infant, and that this effect may be the underlying cause of retrolental fibroplasia. Such a theory would certainly explain many of the clinical findings and conflicting opinions regarding the aetiology of the disease. Thus while the basic injury of vascular obliteration is inflicted in high oxygen concentrations, the effect of this action is not evident until the animal returns to ordinary atmospheric conditions. Consequently, in a sense, those who hold that the disease is due to high oxygen concentrations and those who believe relative anoxia to be the important factor would both, if analogy with the kitten retina is valid, be partly correct.

Many questions remain to be answered and the elucidation of these problems must await further experimental investigation; meanwhile, it is hoped that this demonstration of the profound influence of oxygen on the process of retinal vascularization may assist in narrowing the field of inquiry.

Summary

(1) The development of retinal vessels in the retina of the kitten at birth and for the following 3 weeks is closely comparable to that in the human foetus during the terminal months of intra-uterine life, and, therefore, to that in the premature baby.

(2) In an attempt to assess the role of oxygen in the genesis of retrolental fibroplasia, kittens of a few days old were subjected to a high concentration of oxygen (60–80 per cent.) for several days.

(3) It was found that oxygen in these concentrations has a profound influence on the process of retinal vascularization, and that it may, in certain circumstances, completely obliterate the ingrowing retinal complexes.

(4) Transfer of the animal to air led to a re-opening of the vessels, but many were permanently obstructed, either through collapse or blood clot, so that the normal architecture was not restored. The reformed network was grossly abnormal, haemorrhages occurred, retinal re-vascularization recommenced from the disc, blood vessels grew into the vitreous, and retinal detachment developed.

(5) These phenomena are regarded as significant in the genesis of retrolental fibroplasia in man.

We are indebted to the Medical Research Council for a grant towards the expenses entailed in this work.

Brit. J. Ophthal. (1953) **37**, 521.

EARLIEST SYMPTOMS OF DISEASES OF THE MACULA*†

BY

MARC AMSLER

Zürich

FROM whichever side it is approached, the question of diseases of the macula presents great interest and merits attention, because macular diseases are both common and serious.

Diseases of the macula are common. In the first place I am thinking of senile maculopathy in its various forms. It is beyond doubt that the demographic trend of progressive ageing of the population is producing a very real increase in the number of cases of senile macular degeneration: to such a degree that we find ourselves—as ophthalmologists—involved in the science of " gerontology " and " geriatrics ".

I am thinking, too, of myopia of medium and high degrees, the complications of which frequently compromise central vision long before advanced age is reached.

Even though exudative maculopathies in adults are less widespread, and juvenile and familial macular degeneration is relatively rare, this is not the case in those lesions of the macula which occur in the course of retinopathies associated with hypertension, diabetes, periphlebitis, venous thrombosis, and so on, or again as a complication of chronic iridocyclitis.

Diseases of the macula are serious. In injuring one of man's most precious functions, maculopathies attack him in one of his very sensitive spots, making him not only an invalid, but a particularly unfortunate one. It is certainly not an exaggeration to say that a central scotoma can destroy a professional career and disturb the normal activity of any life.

And what can our therapeutic agents avail against one or other of these progressive lesions of the central retina ? The seriousness of a maculopathy is a direct measure of our impotence to restore vitality to tissues already destroyed, especially to the delicate, highly differentiated sensory or pigmentary epithelium.

METHODS OF INVESTIGATION

Since the invention of Helmholtz (whose centenary we have just celebrated), four or five generations of ophthalmologists have concerned themselves with observing, describing, drawing, and photographing a multitude of morbid conditions of the macula. We have differentiated various ophthalmoscopic pictures, out of which have emerged a corresponding number of morbid

* Received for publication May 21, 1953.
† Montgomery Lecture 1953, Dublin.

states. To distinguish them we have given them names, some of which call up a particular morphological aspect (circinate retinopathy, disciform degeneration, pseudo-tumour of the macula, honeycomb-macula), while others have a pathological significance (central angiospastic retinopathy, central serous choroido-retinopathy, macular capillarosis). Associated with these is a galaxy of famous names, including those of Förster, Hutchinson, Fuchs, Mackay, Nuel, Doyne, Haab, Vogt, Coppez and Danis, Junius and Kuhnt, Horniker, Kitahara, Bailliart, and Duggan.

Glancing at the development and perfection of the methods of investigation of the fundus in general and of the macula in particular, we see, by the second decade of the 20th century, three methods of examination, each complementary to the other, which combine to enrich our knowledge of the morphology of macular lesions.

(*i*) Gullstrand (1911) produced the first binocular and stereoscopic ophthalmoscope which introduced the third dimension into our examination of the macula.

(*ii*) Vogt (1913, 1918) used red-free light the value and usefulness of which even to-day we cannot overestimate: the macula displays its yellow colour more or less intact, and we are able to localize it in the midst of the various lesions which occur at the posterior pole of the eye, the opaque retina concealing any coincident choroidal changes, but, on the other hand, demonstrating clearly the pattern of its fibres and the finest ramifications of its vessels.

(*iii*) Koeppe (1918) gave us the focal illumination of the slit lamp for fundus examination, a technique recently perfected by Goldmann and by Hruby, which enables us to observe the smallest change of level, particularly in the macular region.

What then is the purpose of this achievement of technical perfection if not to allow us to follow, in all their delicacy and intimacy, the changes in the nervous tissues and the vessels at the macula in pathological conditions, and to anticipate, as far as possible, their progress? But here questions of fundamental importance arise.

Does the initial ophthalmoscopic picture of a disease of the macula correspond to the initial visual disturbance which brings the patient to consult us? Do we always find with the ophthalmoscope an organic change at the macula which explains the functional disturbance in question? We all know by experience that this is not the case. An ophthalmologist, no longer amongst us, who was known as a master of accurate ophthalmoscopic observation, one day snubbed a patient who began to describe a recent and subtle visual disturbance: " Please be quiet", he said, " I will soon see what your trouble is ".—" There is nothing the matter " was the verdict after a long and careful examination. But that patient definitely had a disturbance in the form of a slight instability of central vision, a purely functional symptom, which preceded the occurrence, a few months later, of an organic maculopathy, a serious development which I was able to follow myself.

Importance of the Patients' Own Observations

The literature shows that although modern work, founded on the ophthalmoscopic appearances and histopathology of established maculopathies, pays little attention to the functional disturbances which accompany these diseases, older authors, less privileged than ourselves from the technical point of view and undoubtedly less pressed for time, gave much more attention to the explanations and complaints of their patients: they helped them to analyse their visual disturbances, made them draw them, and endeavoured to reconstruct and interpret their subjective symptoms. See, for example, the publications of Förster (1862), Knapp (1869), and Wundt (1898). These old authors interested themselves especially in metamorphopsia as one of the earliest and most characteristic signs of myopic and senile maculopathies. They ask us to do as much.

At Oxford in 1949, I described the case of a patient who replied, after I had told him that he had 6/6 central vision in spite of his complaints: "Yes, I see your small letters, but their quality is missing" (Amsler, 1949).

From this we see that there are *qualitative* disturbances of vision which escape our ordinary quantitative methods of examining central visual acuity. These quantitative examinations, though practical, are on the whole rather crude, for through their apparent precision a visual acuity of 3/6, for example, is compatible with qualitative disturbances of great variety. But it is precisely visual disturbances of this kind, subtle and often transient, which precede ophthalmoscopic changes. Medical science to-day recognizes that in every field functional disturbance precedes the evident organic lesion, and appreciates also that a functional disturbance has more chance of being reversible than an established organic lesion. The old adage *principiis obsta* is of particular value to us, because the sensory organ with which we are concerned lends itself to a self-observation particularly sensitive to the slightest functional failure, and this early failure makes the *principia* on which we should open our therapeutic counter-offensive.

Let us record another fact of everyday experience. This functional disturbance and its variations, provided sufficient attention is paid to it, is a far more sensitive guide to the course of any maculopathy than changes in the ophthalmological picture of the lesion. How often do our patients describe an increase or decrease in visual acuity without our being able to find any ophthalmoscopic sign to account for these changes!

The Early Symptoms of Disease

What then are the first symptoms of diseases of the macula and how can we record them? These early functional symptoms consist on the one hand of *metamorphopsia* (which I shall call *metamorphoma*) and on the other of a *relative scotoma* (which I prefer to call a *translucid scotoma*).

For the purpose of recording these subtle disturbances, our visual charts, with their quantitative scale for distance and reading, are inadequate. How can we reveal the metamorphoma of a high myope who can no longer read

easily, or the scotoma of a patient who persists in rubbing his eye to improve his vision, telling us at the same time this revealing fact: " I should be able to see the letters easily if it were not for the fog in front of my eye ". We should seek methods of following up these clues provided by our patients.

Let us note that these two early symptoms of maculopathy, metamorphoma and relative scotoma, either fail to be revealed by the perimeter and the Bjerrum screen or are recorded inaccurately. Even if we manage to plot a relative scotoma by means of patient exploration with very small targets and low illumination, metamorphoma always eludes a campimetric or perimetric examination. Since it is a matter of making apparent some kind of deformation, we must present to the patient a precise and regular contour which forms as simple a figure as possible, the alterations of which he can assess without difficulty.

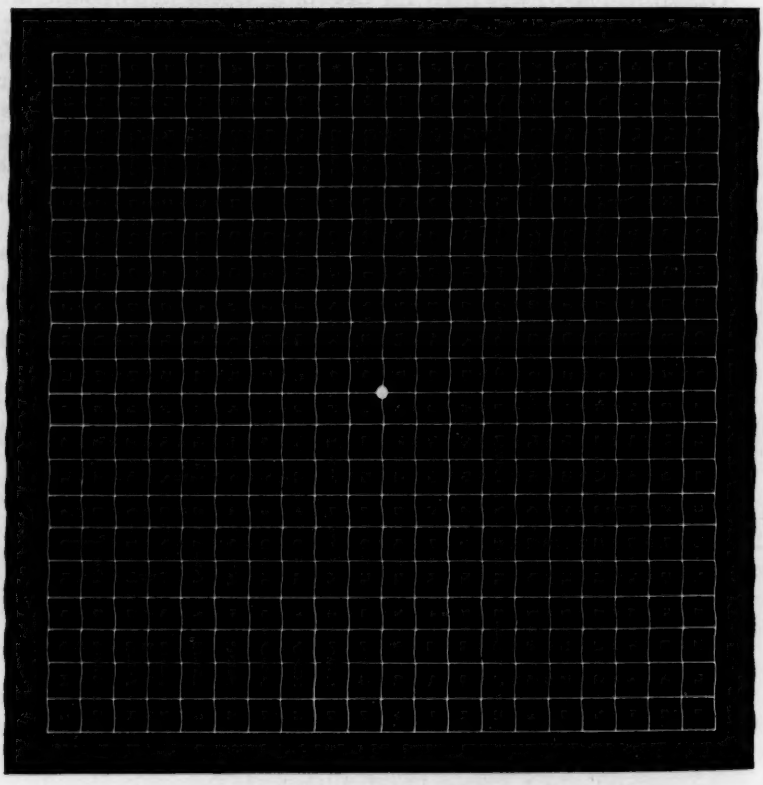


FIG. 1.—The Amsler Grid.

A SIMPLE METHOD OF EXAMINATION

The essential points of a practical and rapid method of examination are these (Amsler, 1947, 1949):

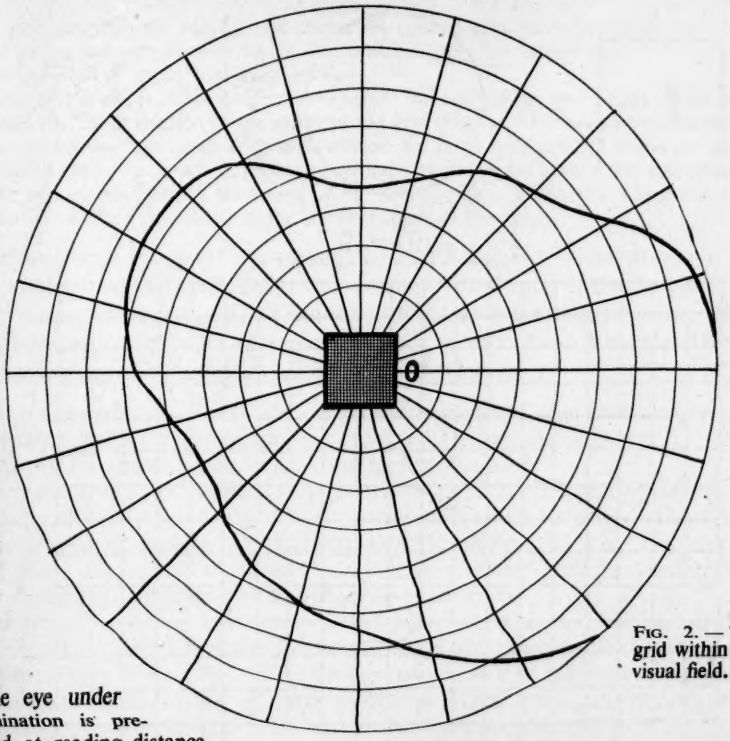


FIG. 2. — The grid within the visual field.

The eye under examination is presented at reading distance (28–30 cm.) with a black card, or better still a school-slate (Fig. 1). On this is drawn in white a 10-cm. square subdivided every 5 mm. by vertical and horizontal parallel lines, thus giving the appearance of a perfectly regular grid. Each small 5-mm. square subtends an angle of 1° at 28–30 cm. distance. The entire grid is thus 20° high and 20° wide, 10° each side of the centre. When it is introduced into the visual field (Fig. 2), its image occupies only a small central area of 10° surrounding the point of fixation, but this area is the most important of the whole. The blind spot lies outside the grid.

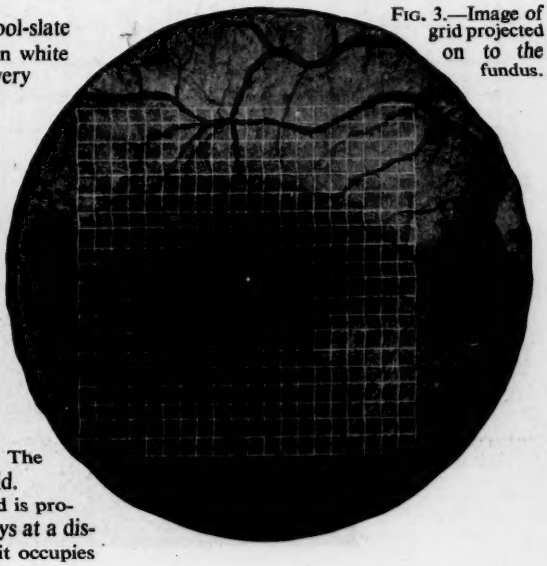


FIG. 3.—Image of grid projected on to the fundus.

When the image of the grid is projected on to the fundus, always at a distance of 28–30 cm. (Fig. 3), it occupies

FIG. 4.—Dimensions and extent of optic disc and macula in relation to the image of the grid.

a greater area than the macula and fovea, the optic disc is found about 5° outside its nasal limits, and only the finest vascular branches (too fine to give rise to the smallest angio-scotoma) penetrate into its projection.

Finally, it is not without interest to consider the dimensions and extent of the optic disc and macula in relation to the image of the grid (Fig. 4). We see here in the middle of the oval fovea, two small concentric circles: the inner one, 200μ in diameter, marks the foveola, the outer, 400μ in diameter, outlines the avascular area of the macula, such as one can see entoptically by means of the Scheerer-Zeiss apparatus, which shows so clearly the capillary circulation in the cerebral layers of the retina.

Returning to the grid* we present it, under a good illumination, to the eye in which we wish to analyse the visual disturbance after the refractive error is carefully corrected. Then we proceed to ask the patient questions: first those which relate to metamorphoma, and then those which are aimed at bringing out the perception of a relative scotoma.

(1) *Metamorphoma.*—"Are the lines which cross in the grid straight and absolutely parallel from beginning to end, especially near the centre?"

"Are all the small squares regular and perfectly equal?"

The patient must, of course, fix the central point of the grid and not let his eye wander, and he must understand what is meant by excentric vision. He will be helped in this by repeated comparison with the other eye. This eye may be healthy and normal and if diseased it will almost certainly not have exactly the same changes in central or paracentral vision as its fellow.

The first thing which strikes us in the course of these examinations is that metamorphoma rarely occupies the entire grid; it almost always occurs in one or sometimes many distinct regions, so that the patient has no difficulty in localizing and determining these foci of metamorphoma which I call, in analogy with scotomata, metamorphomata. The nearer the *metamorphoma* is to the fixation point (it is often central and surrounds it) the easier it is for the patient to observe and describe its character (Figs 5 and 6). There are various forms of metamorphoma; sometimes the lines are broken into small angular irregularities, sometimes they are curved into smaller or greater undulations. The first visual disturbance

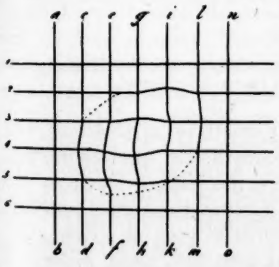


FIG. 5.—The first metamorphoma illustrated in the literature (Förster, 1862).

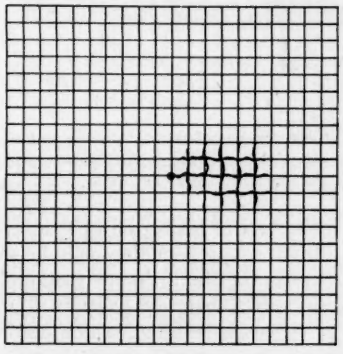


FIG. 6.—Metamorphoma close to the fixation-point; its localization at the right side makes the reading difficult.

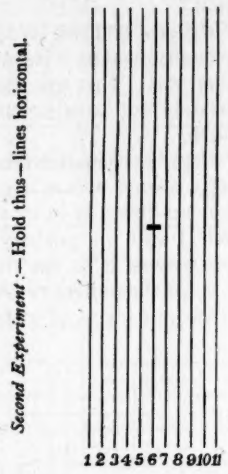
* Which forms a part of a series of seven charts published by Hamblin.

which announces a maculopathy can consist of only one small juxta-central deviation of either the vertical or the horizontal line. If this deviation is found astride the fixation point itself or to its immediate right, it is easy to understand the difficulty in reading.

Sometimes the patient indicates that instead of a definite deformation there is an instability of vision, as if the network of the chart were seen through a sheet of moving water. This also is a manifestation of finest metamorphoma, and is brought about by slight unconscious and involuntary movements of the eye in an effort to see the picture with which it is presented.

A particularly curious phenomenon, already observed and described by Förster (1862) and Mackay (1894), is the orientated metamorphoma. In central or paracentral metamorphoma either the horizontal or the vertical lines only show undulations. To detect this type of metamorphoma, another of my charts presents parallel lines in one direction only, and the patient fixes them successively in the horizontal, the vertical, and the various oblique positions (Fig. 7).

Micropsia, which is fairly frequent, and macropsia, which is rarer, are special types of metamorphoma. Here the metamorphoma is orientated round a centre which is almost always the fixation point. In micropsia (Fig. 8), the vertical and horizontal lines curve inwards toward the central point, in macropsia away from



First Experiment:—Hold thus—lines vertical.

FIG. 7.—The first test-lines illustrated in the literature (Mackay, 1894).

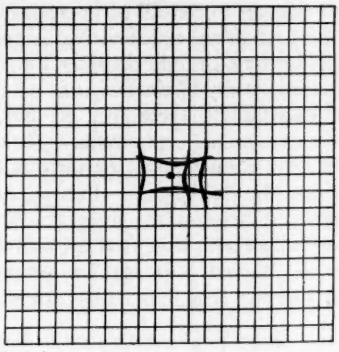


FIG. 8.—Microptic central metamorphoma (macular oedema).

it. The foci of micropsia or macropsia can be very small, occupying only one or two small squares, or they may be much larger, occupying ten lines or more.

In place of the ordinary metamorphomata which the patient localizes within the grid, it sometimes happens that he describes a generalized metamorphoma, more or less orientated, which deforms the entire grid to such an extent that its margins are no longer parallel and its internal lines bent into large, more or less regular, waves. This may be called diffuse metamorphoma.

These different types of metamorphoma correspond more or less to different types of maculopathy.

The small angular defects in the lines of the grid are characteristic of myopic maculopathy; the beginning of senile maculopathy is generally shown by undulations. Diffuse metamorphoma is encountered in detachment of the retina, which starts, for example, as a disinsertion at the ora serrata and spreads to the macular region. When the macula has been detached, and even long after its re-attachment by operation, the patient describes an irregularity of the grid in which the lines look as if they had been drawn free-hand—by an unsteady hand. (Fig. 9).

(2) *Relative, or Translucid, Scotoma.*—" Do you see the grid anywhere perfectly clear and without spots ? "

" Is the region round the central point as clear as the periphery of the grid ? "

(In case there is a spot) " Are the lines in the spot completely absent or only veiled and perhaps interrupted ? "

The net which is thrown, like a butterfly-net, before the patient's eye to catch any visual disturbances sometimes catches a spot which is usually central and circular (or slightly oval or pear-shaped) and which usually measures about 10-12

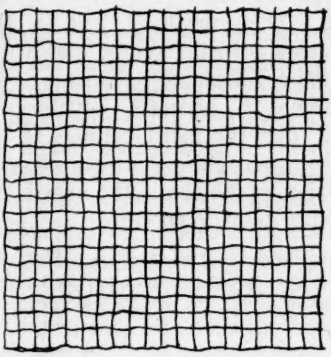


FIG. 9.—Diffuse metamorphoma after a successful detachment operation.

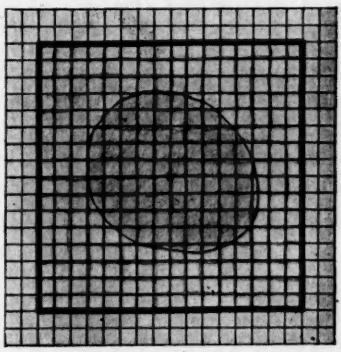


FIG. 10.—Central translucid scotoma, of usual shape and size.

small squares across. This spot is translucid; it does not completely hide the crossing lines of the grid but covers them with a veil which is sometimes homogeneous and sometimes more opaque in one place than in another. It is the presence of this translucid central scotoma which gives rise to the patient's habit of rubbing his eye in a vain effort to improve his vision (Fig. 10).

This translucid scotoma can also be excentric, when it is smaller and often multiple; the patient indicates these spots, which are irregularly placed, with his finger. The farther these spots are from the centre, the greater his difficulty in determining their shape.

It often happens, in either the first or subsequent examinations, that the patient shows a combination of metamorphoma and translucid scotoma. This combination may be made up of many variations. Sometimes the metamorphoma, especially the microptic type, coincides with the scotoma so that lines are only

distorted within the translucid scotoma; sometimes the metamorphoma is appreciated in a more or less circular zone surrounding the scotoma; sometimes metamorphomata occur quite independently of the central translucid scotoma.

Underlying Pathology

Let us now turn to the significance of these metamorphomata and translucid scotomata and ask ourselves what is the *structural basis* underlying them. Histopathology will never help to solve this problem. Even if we had the opportunity to examine a macula microscopically at this stage, death, chemical fixation of the globe, and the manipulations of the laboratory would certainly have destroyed or fundamentally modified the delicate microstructure of the macular retina and its sensory elements. Nor can the early stages of these symptoms be established by an examination of sections of established macular lesions.

In point of fact, it is at the level of the pigmentary epithelium and the sensory epithelium of the macular retina, which together make up the anatomico-physiological couple of visual perception, that we must look for the organic basis of metamorphomata. They result, I believe, from a displacement of the perceptual elements of the retina and a false localization of the image seen by these displaced elements. This pathogenic explanation of metamorphoma is generally attributed to Förster, but Mackay (1894) pointed out that the merit belongs to Reid who explained in this way his own metamorphoma which caused a considerable disturbance after he was dazzled by the sun in the course of an astronomical observation in 1761. Here are Reid's own words:

> . . . A straight line appears to the right eye to have a curvature in it. Thus, when I look upon a music book, and, shutting my left eye, direct the right eye to a point of the middle line of the five which compose the staff of music, the middle line appears dim indeed at the point to which the eye is directed, but straight; at the same time, the two lines above it and the two below it appear to be bent outwards, and to be more distant from each other and from the middle line, than at other parts of the staff to which the eye is not directed (Reid, 1801).

Reid advanced the following hypothesis to explain the curving of the lines of the staff of music:

> To me it seems probable that a small part of the retina towards the centre is shrunk, and that thereby the contiguous parts are drawn nearer to the centre and to one another than they were before, and that objects whose images fall on these parts, appear at that distance from each other which corresponds not to the interval of the parts in their present preternatural contraction, but to their interval in their natural and sound state.

It was not until one hundred years later that Förster reached a similar conclusion: when two parallel lines are separated from each other by an outward curve it means that the retinal elements are approximated to each other at this point. Macropsia is thus the outcome of retinal contraction.

Micropsia, always present in central serous choroido-retinitis (Oguchi, 1922; Kitahara, 1936; Horniker, 1927; Bonnet, Paufique, and Bonamour,

1939; Streiff, 1939; and above all Brückner and Field, 1945), is the opposite case. The oedema raises and distends the basal attachment of the cones and separates them so that fewer perceptive elements are stimulated; thus the object appears smaller than it really is, and micropsia results.

What is it which displaces and separates the elements of the sensory epithelium of the macular retina? There is no doubt whatever that it is a fluid agent. These metamorphomata of changing dimensions and shape, which disappear and re-appear, can only be due to the action of a liquid. On the other hand, we know that amongst the most constant changes, histopathology of advanced macular lesions shows spaces, lacunae, cysts, and other formations, where during life fluid collects or possibly circulates.

What is this fluid and where does it come from? In the first place, we must postulate an oedema produced from the chorio-capillaris, the outcome of a transudation or exudation through the changed walls of the capillary network which nourishes directly the pigmentary and the visual epithelium. The chorio-capillaris is modified by the senile changes of sclerosis and its walls become permeable. The fluid which transudes into the sensory retina displaces the perceptual elements and gives rise to metamorphomata.

We can visualize, in an analogy with our knowledge of oedema elsewhere in the body, that the fluid which displaces the macular cones can be more or less harmless or dangerous according to the nature of its contents, and a toxic factor can be added to the mechanical element. A purely mechanical oedema can be re-absorbed rapidly and will produce a transitory metamorphoma; the other type of oedema, toxic in character, permanently injures the macular cones after having broken up their regular arrangements: in this case the metamorphoma becomes an absolute scotoma.

The pathological fluid can also arise more directly from the pigmentary epithelium itself, which Magitot considers to be a secretory organ, the activity of which, nevertheless, is also conditioned by the chorio-capillary circulation. Perhaps the senile hyaline secretion (Magitot) of the pigment epithelium also plays a role in the disturbance of the macular cones.

Finally, the fluid responsible for a metamorphoma could also be extravasated blood, once again coming from the chorio-capillaris. We are aware of the frequency of deep haemorrhages during the ophthalmoscopic progress of senile and myopic maculopathies. We know also that a choroidal haemorrhage is far more dangerous to the visual function than a true retinal haemorrhage because in the deeper layers the sensory cells themselves are bathed in blood.

In addition to the " fluid " factor and in connection with it, one must bear in mind the sclerotic changes and hyaline degeneration of the chorio-capillaris: the vessel walls become thickened and their lumen narrowed, and to compensate for this other capillaries are dilated. Often there is a general condition of pre-capillary spasm. In these conditions it is not surprising that the sensory epithelium of the retina becomes disorganized; this disorganization becomes apparent in metamorphomata.

Let us now turn to the structural basis of the purely central translucid scotoma, that is to say, a scotoma without metamorphoma such as may appear at the very beginning of certain maculopathies.

Once again it is an oedema, localized this time not in the deep perceptual layers of the retina (where it would displace the cones) but in the conducting layers the structure of which at the macula is so highly specialized. Duke-Elder (1940) points out clearly that "the structure of the thick fibre-layer of Henle, with its ability to swell, can absorb large quantities of fluid". It is this oedema situated in front of the sensory layer of the retina which appears to the patient as a veil or mist in front of his eyes and which he tries to get rid of by rubbing them.

In the origin of this oedema it is the circulatory system of the cerebral layers of the retina, the system of the arteria centralis retinae, which plays the great part. In point of fact, a central translucid scotoma is only rarely encountered in the early stages of myopic maculopathy, but as a rule is the precursor of the macular lesion in those retinopathies which one knows to involve the cerebral layers of the retina, of which malignant hypertensive retinopathy is a prototype. Here, also, the oedema can be more or less mechanical, "circulatory", and harmless to the retinal fibres, or, on the contrary, exudative, "inflammatory", and toxic in nature, bringing in its train irreversible disturbances of conduction.

The formation of the oedema here also is linked with circulatory disturbances due to arteriolosclerosis, which is often accentuated by a spastic condition of the retinal pre-capillaries, seen by the ophthalmoscope. I attribute a localizing significance to the two symptoms we have been discussing—pure metamorphoma and pure translucid scotoma. Each tells us in which part of the macula the disease begins, whether it is in the deep sensory complex lying on the nutritive chorio-capillaris, or in the superficial conducting part of the retina, the layer of Henle. The fact that sooner or later the patient experiences metamorphomata and scotomata simultaneously shows us that the two stages of the disease—the two areas of oedema and structural change soon merge—so that they involve all the tissues of the macula.

The macula is not only a tenuous part of the retina, but is itself an entity consisting of two parts, the deeper which is choroidal and shares pathological changes with the choroid, and the more superficial which is entirely retinal. Ophthalmoscopically, these two parts of the macula and their diseases are distinguished from each other by a very important element: the pigment.

In all deep maculopathies which from the onset give rise to metamorphomata, the ophthalmoscope sooner or later demonstrates irregularities of pigmentation; these are often very slight—at the beginning a hardly perceptible scattering which is not demonstrable in red-free light—but they are shown up by a concentrated beam of the usual ophthalmoscopic light focused a little to the side of the suspected region. On the other hand, in the

maculopathies affecting the cerebral layers of the retina there is no pigmentary disturbance. The pathological process lies anterior to the perceptual layers of the retina, in the conducting layers. The integrity of the sensory epithelium shows itself functionally by the absence of metamorphoma and ophthalmoscopically by the absence of pigmentary changes.

One more important functional symptom of maculopathy is the absolute scotoma. I have not mentioned it until now because an absolute scotoma is not an early symptom, but a final one which results from the destruction and death either of the perceptual retinal elements or of the conducting fibres. It is true that, in the relatively early stages of myopic maculopathy, minute absolute scotomata may accompany the small broken metamorphomata which characterize the visual disturbance of high myopes. But even in this case there always is an initial stage of pure metamorphoma. On the other hand, in the spread of a cerebral retinopathy to the macula, the central translucid scotoma is usually not transformed into an absolute scotoma; for this to happen, the deep sensory retina must eventually be involved, or the oedema-fluid particularly toxic.

TREATMENT

The considerations put forward in this attempt to systematize the early functional disturbances of the macula, may appear somewhat hypothetical and speculative. They have been suggested by experiments with the grid and clinical experience over some 25 years. It is hoped to stimulate renewed interest in the early qualitative alterations in central vision, because the diagnosis of a very early functional symptom at a stage before the appearance of the first ophthalmoscopic changes presents therapeutic opportunities which no longer exist when a destructive lesion has become established. Metamorphoma and relative scotoma, the initial functional symptoms of the maculopathies are, in fact, often reversible, and may diminish or even disappear with appropriate treatment.

REST.—The treatment to be put into effect as soon as a functional disturbance symptomatic of a maculopathy is diagnosed must, above all, ensure complete rest for the affected macula.

To understand this fundamental necessity, we must try to picture in all their complexity the biochemical changes and bioelectrical reactions which take place in the functionally active retina and especially in the macula which is so highly differentiated.

To rest the macula means a prolonged cessation of all visual activity and the protection of the eyes from bright light: this is not at all easily acceptable to a man or woman who is suddenly afflicted in the height of a full professional life by a visual disturbance still slight in degree and affecting one eye only, but the patient must understand the importance of an early and drastic treatment designed to be abortive in the eye already affected and preventive in the other eye.

This therapy by ocular rest is certainly more easily obtained in the discipline of the hospital than in the home. In hospital, resting the eyes can form part of a general therapeutic plan of rest, for such patients are usually overworked; the diet can be supervised, the use of alcohol and tobacco controlled and restrained, and above all psychotherapy can be put into practice. Often, however, circumstances force us to begin treatment while the patient is ambulatory, and this continues until the patient himself notices that his condition is deteriorating and becomes aware of the necessity of hospital treatment.

GENERAL PHYSICAL EXAMINATION.—Whether it is a myopic or senile maculopathy that is beginning, it is essential for the patient to undergo a general examination, particularly from the cardiovascular point of view. Special attention must be paid to the peripheral vessels and to any abnormalities in the capillary circulation. A search must be made for foci of infection, and if found, they should be treated radically.

DRUGS.—Treatment by drugs should follow our present concepts of the physiology and pathology of the capillary circulation; for these we are indebted in the first place to the classical work of Bailliart, beyond which we resort to empirical measures.

Vasodilators.—Our principal therapeutic agent, which is directed against the spasm and obstruction of the smaller vessels which bring about and dominate the pathological condition of the macula, includes all the various vasodilators at our disposal. Primarily, these are acetylcholine, a hormone, and nicotinic acid, a vitamin of the B group, and their derivatives under whatever pharmacological name they may masquerade. "Ronicol", for example (a Roche preparation) contains as its active principle, B.pyridycarbinol, an equivalent of nicotinic acid, 25 mg. per tablet.

In the case of an incipient maculopathy, the vasodilators are only very rarely given by local injection or in massive doses (such as would be given to relieve an acute spasm of the central retinal artery); they are given by mouth in relatively small doses repeated over a very long period. Thus we order 2 to 3 tablets of Ronicol to be taken daily for a period of 8 to 10 days. After this we give a suppository containing 0·2 acetylcholine each evening for 4 to 5 days. Then again Ronicol followed by acetylcholine and so on. It goes without saying that the two drugs can be given at the same time or in another rhythm or in combination with some other vasodilator, such as Priscol (Ciba).

In addition to these known vasodilators a classical lotion is prescribed, potassium iodide 1 per cent. (Jean-Gallois, 1952). We prescribe regularly sodium iodide 1 per cent. and calcium chlorate 1 per cent., instilled daily or twice daily, and continued over a considerable time. Short waves can also contribute by producing a hyperaemia of the ischaemic macula.

The effects of these therapeutic measures cannot be observed by the

ophthalmoscope; it is the patient who will indicate on our grid the changes which occur in his metamorphomata or translucid scotomata. The functional criteria matter more than the ophthalmoscopic. And even if there is a macular lesion to be seen, the subjective indications of the patient, provided they are in the slightest degree precise, tell us far more about the effect of our therapy than the ophthalmoscopic picture, which seems often to be stationary.

Anti-exudatives.—As soon as the maculopathy shows itself by a central micropsia or a central translucid scotoma—two symptoms of oedema, accompanied sometimes in their early stages by the minute ophthalmoscopic sign of the disappearance of the foveolar reflex—we must begin a treatment aimed at diminishing the permeability of the capillary walls and aiding the resorption of the extravasated interstitial fluid.

Injections.—It is here that calcium given by intravenous or intramuscular injection may prove of value. We must remember, however, that the effect of calcium does not last more than 2 hours, a fact demonstrated by our work on the fluorescein-test in man. Injections should therefore be given right away and repeated morning and evening over many days and in rather strong doses (10-20 ml. of a 10 per cent. solution intravenously, or 10-20 ml. of a 20 per cent. solution intramuscularly).

Another drug which may perhaps help even in advanced cases of macular oedema as a retrobulbar injection is atropine (Bangerter, 1945). A 1 per cent. solution of atropine is injected 2 to 3 times a week in increasing doses from 0·3 to 0·6 ml. and up to twelve injections.

This treatment by retrobulbar injection brings me to the discussion of local therapy in general. Myopic maculopathy and senile maculopathy in all its forms are spontaneously progressive diseases. If they are taken in hand at the beginning, as we can do with our accurate method of examination, these diseases, though they cannot always be cured, can at least be improved or arrested for a time. This does not mean that our treatment always achieves these results. The disease can progress, the metamorphoma spread, or the scotoma thicken, in spite of all our therapeutic efforts. It can thus happen that our patient becomes aware of a deterioration of vision following, for example, a subconjunctival or retrobulbar injection. From then on, his reasoning *post hoc propter hoc* can make him refuse, perhaps regrettably for ever, the continuation or resumption of any further local treatment. It is unwise to discount this psychological factor, and it is therefore better to begin with extra-ocular medicaments (if I may call them this), to which no harmful effect can be attributed in case of an aggravation of symptoms during the first phase of the treatment.

Vitamins.—If a maculopathy occurs in a patient who has a tendency to haemorrhages, whether from fragility of the capillaries or delayed blood coagulation, recourse should be made to appropriate remedies: Rutine and

Vasorutine, which are the fashion to-day but whose mode of action (reinforcement of the capillary walls?) and efficacy, as you know, are in dispute, vitamin C, vitamin K, calcium, Adrenoxyl, and so on.

A popular belief opens up the possibilities of another therapeutic field. With us carrot juice is popularly believed to improve weak sight, and in recent years many of our patients have affirmed good effects from fresh carrot juice taken each morning. This empirical remedy merits serious consideration of the possible value to the retina of vitamin A, the "vitamin of the eye" *par excellence*, which is essential to the metabolism of visual purple, and which, according to recent research, is found not only in the rods but also in the cones, and particularly in the specialized sensory elements of the fovea.

Consequently it can be recommended at the onset of a maculopathy with metamorphomata localized to the physiological couple sensory epithelium and pigment epithelium, to prescribe a vitamin preparation such as "Arovit" (Roche), for example, in doses of two or three pills of 50,000 international units daily.

But it is not vitamin A alone which is important in the early treatment of maculopathy. Vitamin B_1, aneurine, which activates the metabolism of glucose and increases the oxygen consumption of the cell; Vitamin B_2, riboflavine, which enters into the formation of the enzyme of the yellow ferment of cellular oxydation and which has been found abundantly in the visual cells and pigmentary epithelium, and above all vitamin C, ascorbic acid, an important factor in cellular oxydation and reduction and also in the nutrition of the capillary endothelium—all these vitamins play a definite or at least an accessory role in our macular therapy.

There are preparations containing all these vitamins, such as, for example, "Protovit" (Roche) or "Nestrovit" (Roche) which simplify vitamin treatment considerably.

TISSUE THERAPY.—The last therapeutic measure to be discussed is very complex in nature and obscure in its action: the placenta, placental extract, and placental blood serum.

The tissue-therapy of Filatov, already 20 years old, has its greatest indication in pigmentary degeneration of the retina. All who have a personal experience of this treatment have seen, as I have, some slight functional successes and many failures. In our clinic at Zürich only a few young patients reacted favourably, in whom the tapeto-retinal degeneration was not too advanced and which still showed signs of deterioration. This evidence encouraged us to use tissue-therapy at the beginning of a maculopathy and before an irreversible lesion occurred in the central chorio-retina.

How does the placenta implanted or injected under the conjunctiva act? What are the active elements? Are they the "biogenic stimulines" of Filatov liberated by a dead tissue? Are they the various and many hormones of the placenta and the serum of fresh placental blood, as we use it ourselves? Is it just simply the hyperaemia and vasodilatation caused by the implantation or the injection which causes a therapeutic effect?

It is impossible so far to reply to these questions. Whatever the answer may be, it is sufficient for the present that there is a probable or possible stimulatory action on the retina, which is worth considering also as a therapeutic agent for the circulatory and trophic disturbances which occur so frequently and are so serious in the maculopathies of myopia and old age.

Vasodilators, anti-exudatives and re-absorbents, anti-haemorrhagics, vitamins, and hormones—here is a well-stocked therapeutic arsenal. But once again, what can all these arms do against a spot of Fuchs, a disc of Junius-Kuhnt? There is nothing more disillusioning than an established macular lesion.

Importance of Early Diagnosis and Treatment

But every maculopathy has a beginning. It is this beginning which the patient sees and experiences. It is this beginning which we can record on the functional level of symptoms which are susceptible to treatment. Let us imagine the dismay of a man who is beginning to lose his central vision and to suspect with anxiety what the future has in store for him, and is told that "the early detection of macular degenerations is not of great importance, as we can do nothing for them" (Zentmayer, 1938).

On the other hand if he were told: "we are going to endeavour to remedy your ocular disease at the very onset, and, though unable to promise you anything for certain, we are going to try every method we know to improve your capillary circulation and to rest, protect, and nourish your retina", he would be happy. And grateful, even if he saw his doctor groping in his choice of drug or combination of drugs to which the retina would respond; grateful even if the therapeutic effect did not last . . .; grateful for his doctor's perseverance at least in trying.

To conclude, the opposite proposition may be affirmed: "The early detection of macular degenerations is of great importance, as we can do something for them".

REFERENCES

Amsler, M. (1947). *Ophthalmologica, Basel*, **114**, 248.
——— (1949). *Trans. Ophthal. Soc. U.K.*, **69**, 397.
Bangerter, A. von (1945). *Ophthalmologica, Basel*, **109**, 102.
Bonnet, P., Paufique, L., and Bonamour, G. (1939). *Ann. Oculist., Paris*, **176**, 560.
Brückner, R., and Field, N. H. (1945). *Ophthalmologica, Basel*, **109**, 281.
Duke-Elder, S. (1940). "Text-book of Ophthalmology", vol. 3, p. 2592. Kimpton, London.
Förster, R. (1862). "Metamorphopsie. Ein Symptom partieller Schrumpfung der Retina (*Retinitis circumscripta*)". Ophthalmologische Beiträge, Berlin.
Gullstrand, A. (1911). *Arch. Augenheilk.*, **68**, 101.
Horniker, A. (1927). *Ann. Ottal.*, **55**, 578.
Jean-Gallois (1952). *Bull. Soc. Ophtal. franç.*, Suppl. 6.
Kitahara, S. (1936). *Klin. Mbl. Augenheilk.*, **97**, 345.
Knapp, H. von (1869). *Arch. Augenheilk.*, **1**, 1, 6.
Koeppe, L. (1918). *Münch. med. Wschr.*, **65**, 391.
Mackay, G. (1894). *Ophthal Rev.*, **13**, 1, 41, 83.
Oguchi, C. (1922). *v. Graefes Arch. Ophthal.*, **110**, 25.
Reid, T. (1801, 1st ed. 1764). "An Inquiry into the Human Mind on the Principles of Common Sense", 5th ed., p. 275. Millar, London. *Quoted by* Mackay (1894).
Streiff, E. B. (1939). *Klin. Mbl. Augenheilk.*, **103**, 524.
Vogt, A. (1913). *v. Graefes Arch. Ophthal.*, **84**, 293.
——— (1918). *Klin. Mbl. Augenheilk.*, **6**, 379.
Wundt, W. (1898). *Philos. Stud.*, **14**, 1.
Zentmayer, W. (1938). *Delaware St. med. J.*, **10**, 33. *Quoted by* J. V. V. Nicholls (1952). *Amer. J. Ophthal.*, **35**, 1753.

Brit. J. Ophthal. (1953) **37**, 538.

VISUAL ACUITY AND THE CONE CELL DISTRIBUTION OF THE RETINA*

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BOTH Polyak (1941) and Ludvigh (1941) have discussed the acuity gradient of the visual field and its relation, among other matters, with the structure of the retina. In general, for photopic vision, the relevant structural characteristics of the retina include the regional variations of (*i*) the size and the separating interval of the cones, and (*ii*) the ratio of the number of cones to that of the optic nerve fibres (Polyak, 1936) referred to as the convergence ratio. Polyak and Ludvigh have compared the acuity gradient of the visual field with the gradient of the cone-cell intervals in the retina, and have shown that to some extent they are closely similar. In this paper some details are discussed which arise as a result of their work.

THE WORK OF POLYAK AND LUDVIGH

The curves 1*a* and 1*b* of Fig. 1 (opposite), including the ordinate scale shown on the left, are reproduced from Polyak's comprehensive monograph on the retina (1941, Fig. 99). These curves have since appeared in the writings of Ruch (1946) and Adler (1950), and are now widely known. The curve 1*a* shows the angular intervals between adjacent cones, whilst curve 1*b* represents the visual acuity, both of which are plotted against the angular displacement from the centre of the fovea and of the visual field. With reference to these curves Polyak (1941, p. 436) writes that the cone intervals '. . . form a curve similar to the visual acuity curve of Wertheim and others', and quotes Emsley (1936) as the source of visual acuity data. Emsley specifically acknowledges Wertheim (1894) as the source of his quantitative data.

In Fig. 2, the curve 2*a* is reproduced from the results of Wertheim's experiments in which wire gratings were used ; it shows the variation of the mean of the nasal and temporal values acuity in the horizontal meridian of the visual field. Wertheim recorded his results as relative values of acuity, the centre of the field having a maximum value of unity, and the peripheral zones having smaller values which ultimately reach zero.

If one now compares the curves 1*b* and 2*a*, it will be seen that they are almost identical, and that in fact the curve 2*a* has been directly superimposed upon Fig. 1. The ordinate scale of Fig. 2 has been drawn on the right hand side of Fig. 1 to facilitate this comparison. If a graphical comparison of Wertheim's acuity values in Fig. 2 (ranging from unity in the centre of the field to zero at the extreme periphery) is to be made with the cone intervals in Fig. 1 (ranging from 24″ in the centre of the fovea to approximately 3′ 40″ at the ora serrata), it is essential first to transform one of these sets of values so that it can be inserted in the co-ordinate system of the other. It would appear that Polyak has overlooked the necessity for allowing for the dissimilarity in the co-ordinate systems of Figs 1 and 2.

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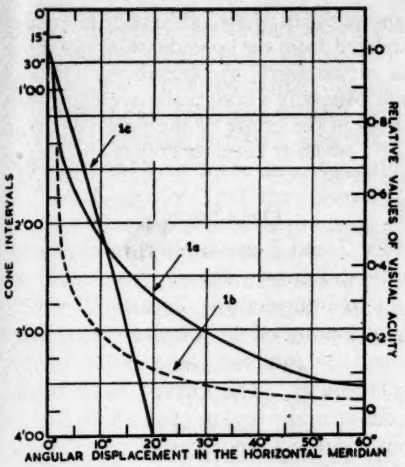

FIG. 1.—Curve 1*a* indicates the variation of the cone cell intervals with angular displacement from the centre of the fovea (Polyak). Curve 1*b* shows the variation of the visual acuity with angular displacement from the centre of the visual field in the horizontal meridian; the right-hand ordinate scale is only for comparison with the curve 2*a* in Fig. 2 as described in the text. Curve 1*c* is Wertheim's acuity curve in terms of the left-hand ordinate scale.

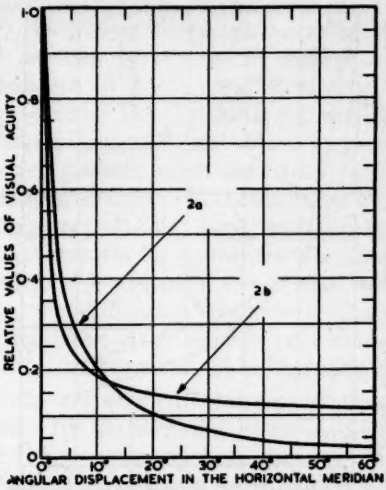

FIG. 2.—Curve 2*a* shows the variation of the visual acuity (Wertheim), and is the mean of the nasal and temporal values in the horizontal meridian of the visual field. Curve 2*b* is the variation of the cone cell intervals (Polyak) in terms of this ordinate scale.

In the central fovea, the smallest cones are separated by intervals almost as small as 1μ between their centres; Polyak estimates this as equivalent to 12″–15″, and occasionally more specifically as 12″, corresponding to a first focal length of 17·2 mm. for distant vision. In a central area 100μ in diameter, there are some 2,000 cones which have an average interval between centres of 2μ, or 24″ (Polyak, 1941, p. 425). The value of 24″ is therefore used as the average cone interval for 0° displacement in curve 1*a*. Thus, if a unity value of acuity is to correspond with a central foveal cone interval of 24″, then each relative value of acuity must be first divided into 24″ before inserting it in Fig. 1. In other words, if any of Wertheim's acuity values is denoted by w, it must be first altered to $24''/w$, before transposing it from Fig. 2 to Fig. 1. As a result of this transformation we obtain the curve 1*c*, and it is in this form, not as in curve 1*b*, that Wertheim's acuity values should be contrasted with the cone intervals of curve 1*a*. Or, alternatively, if Polyak's cone intervals are denoted by p seconds of arc, they can be inserted in Fig. 2 by first transforming them to $24''/p$. Curve 2*b* then follows as a result, and the two curves 2*a* and 2*b* provide an alternative comparison of acuity and cone intervals within the co-ordinate system of Fig. 2.

The curves in Fig. 2 now resemble to some extent the results obtained by Ludvigh (Fig. 3, overleaf). The curve 3*a* is the variation of the acuity, out to a maximum displacement of 10°, as determined by Ludvigh using selected Snellen letters. It is moderately similar to Wertheim's results shown in curve 2*a*. Curve

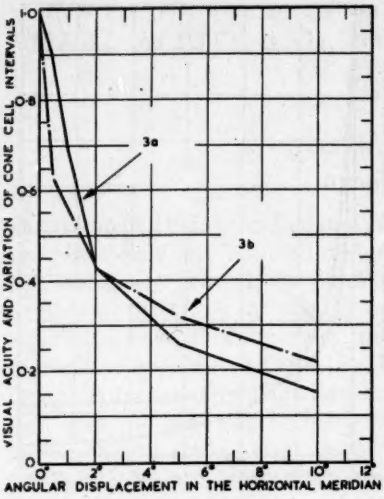

FIG. 3.—Curve 3*a* shows the variation of the visual acuity (Ludvigh). Curve 3*b* gives the variation of the cone cell intervals (Østerberg).

3*b* shows the variation of the cone intervals calculated from the cone densities per unit area determined by Østerberg (1935). From Østerberg's results the average cone interval in the centre of the fovea is 2.6μ, or 31″, which is close to Polyak's average value of 24″.

DISCUSSION

Figs 2 and 3 are similar, in that the acuity and cone interval curves have a point of intersection; 2*a* and 2*b* intersect at a point of 12° displacement, and 3*a* and 3*b* intersect at a point of 2° displacement. The curves have steep gradients in the region of small displacements, and relatively small discrepancies will therefore produce large differences in the position of this point of intersection. Polyak's work on the size and distribution of the cones in the retina is later and more detailed that that of Østerberg, and for this reason it is possible that Fig. 2 is more reliable than Fig. 3.

The fact that a point of intersection occurs is the surprising feature of Figs 2 and 3. Polyak (1941, p. 426) explains the difference between curves 1*a* and 1*b* as due to an increase in the size of the functional cone unit in the extra-foveal zones of the retina, *i.e.* the cones become linked with increasing multiple synaptic relations and as a result they tend to function in groups rather than as individuals. But if, more correctly, we now use the curves 1*a* and 1*c* (similarly, 2*a* and 2*b*, and 3*a* and 3*b*), this explanation can only hold for displacements greater than the point of intersection. For displacements less than the point of intersection, the curves would seem to suggest that the details resolved in the visual field have angular dimensions smaller than the cone intervals. Cone cells respond *in toto* to a light stimulus (Polyak, 1941, p. 423), and it is highly unlikely that they possess a structural subdivision permitting the resolution of detail more fine than that of the cone cell intervals. One would therefore expect to find that the acuity curve lies either on or beneath the cone interval curve, and that a point of intersection can occur nowhere. The problem is therefore to find how the curves have been wrongly contrasted.

When discussing visual acuity, it is first necessary to distinguish between the minimum perceptible (minimum perceptibile) visual angle and the minimum resolvable (minimum separabile) visual angle. Various experiments have shown that objects are visible even when they subtend extremely small angles.

For example, Hecht and Mintz (1939, 1947) have shown that wires having diameters subtending 0·5″ to 0·6″ of arc can be perceived. This is not surprising when we remember that Arcturus (α Bootis) and Betelgeuse (α Orionis), the fifth and twelfth brightest stars in the sky, have angular diameters as small as 0·047″ and 0·022″, respectively. Objects subtending such small angles as these appear as diffraction patterns upon the retina; for a point source of light the centre of the diffraction pattern consists of a disc, receiving 84 per cent of the radiant energy entering the pupil, and having a diameter of approximately $\theta = 2{\cdot}44\,\lambda/d$, where d is the diameter of the pupil. White light has an effective wavelength of 556μ, and if $d = 3$ mm., then $\theta = 1{\cdot}55'$. However small the object, the diffraction image will remain unchanged in size, and the minimum perceptible visual angle is only limited by the light intensity of the source and the brightness of the background.

The acuity curves 2*a* and 3*a*, however, are derived from the minimum resolvable visual angle. Raleigh's criterion for the minimum angle of resolution is $\theta = 1{\cdot}22\,\lambda/d$, and using the previous values, we have that $\theta = 46''$. Unfortunately, Wertheim does not record the resolutions corresponding to his relative values of acuity, but if we suppose that 46″ corresponds to his unity value of acuity for the centre of the visual field, the error should not be large. Using the relation $p = 46''/w$, we obtain the curve 4*a* in Fig. 4, which is Wertheim's experimental result now expressed in terms of the minimum resolvable visual angle. Curve 4*b* is Polyak's cone interval curve 1*a*, and it can now be seen that there is no point of intersection between the two curves. Finally, curve 4*c* gives the ratio of the resolution to the cone intervals, in terms of the right-hand ordinate scale.

For displacements greater than 3°, the ratio of the resolution to the cone intervals progressively increases, and possibly has some close relation with the convergence ratio of the cone cells to the optic nerve fibres. For displacements of less than 3°, the ratio is again larger than unity, rising to a value of 1·9° for zero displacement. Polyak (1941, p. 221) describes the foveal photoreceptors as having monosynaptic relations with the conducting neurons, and states (p.

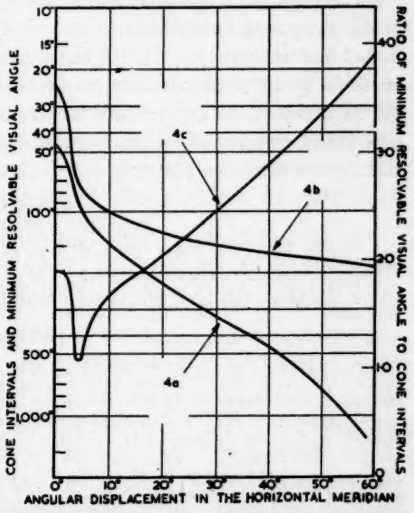

FIG. 4.—Curve 4*a* is the visual acuity (Wertheim) assuming that a unity value corresponds to a minimum resolvable visual angle of 46″. Curve 4*b* shows the variation of the cone cell intervals (Polyak). Curve 4*c* is the ratio of the minimum resolvable visual angle to the cone cell intervals.

425) that each cone is an almost independent functional unit. The increase in the ratio in this region must therefore have a different explanation from that which accounts for large displacements.

One possibility is that Wertheim was unable in his experiments to resolve the finest detail in the centre of the visual field. This would seem to be the most likely explanation, for, *a priori*, one can see no reason for the centre of the retina possessing a degree of refinement in its cone structure, equal to or better than that shown in 4*b*, unless it is for the purpose of resolving discriminate detail in the visual field. Wertheim extrapolated his results from $\pm 2{\cdot}5°$ to 0° displacement; Weymouth and others (1928) and Jones and Higgins (1947), however, have made measurements within this range and have found relative values of acuity having a gradient approximately the same as Wertheim's. In one case, Weymouth and others found that the minimum resolved angle was 40″. Shlaer (1937) determined experimentally the relation between visual acuity and illumination, and for a maximum illumination found that the minimum resolved angle was 28″. This would correspond to a ratio of 1·13 in curve 4*c* for zero displacement. Using Lagrange's law, with a value of 1·337 for the refractive index of the vitreous humour and a magnification of 0·923 between the entrance and exit pupils of the unaccommodated eye (Hardy and Perrin, 1932), we obtain $\alpha' = \alpha\, 1{\cdot}235$ where α and α' are the angles subtended in the object and image spaces respectively. Thus Shlaer's value of 28″ becomes 22·7″ in the image space of the eye, corresponding to a zero-displacement ratio of 0·95 for curve 4*c*.

A cone interval of 12″ is equivalent to 14·8″ in the visual field, and it remains to be seen whether more refined techniques in visual acuity experiments are capable of yielding minimum resolvable visual angles approaching this value, in spite of eye movements, dioptric aberrations, and the diffraction effect produced on the retina.

Summary

Polyak and Ludvigh have compared graphically the acuity gradient of the visual field with the gradient of the cone separating intervals in the retina; some details arising from their results are discussed.

REFERENCES

ADLER, F. H. (1950). " Physiology of the Eye ", fig. 291, p. 634. Kimpton, London.
EMSLEY, H. H. (1936). " Visual Optics ", fig. 2.12, p. 51. Hatton Press, London.
HECHT, S., and MINTZ, E. U. (1939). *J. gen. Physiol.*, **22**, 593.
——— ROSS, S., and MUELLER, C. G. (1947). *J. opt. Soc. Amer.*, **37**, 500.
HARDY, A. C., and PERRIN, F. H. (1932). " The Principles of Optics ", p. 188. McGraw-Hill, New York.
JONES, L. A., and HIGGINS, G. C. (1947). *J. opt. Soc. Amer.*, **37**, 217.
LUDVIGH, E. (1941). *Amer. J. Ophthal.*, **24**, 303.
ØSTERBERG, G. (1935). *Acta ophthal., Kbh.*, **13**, Suppl. 6.
POLYAK, S. (1936). *Arch. Ophthal., Chicago*, **15**, 477.
——— (1941). " The Retina ". University of Chicago Press, Chicago.
RUCH, T. C. (1946). In " Howell's Text-book of Physiology ", ed. J. F. Fulton, 15th ed., fig. 262, p. 486. Saunders, Philadelphia.
SHLAER, S. (1937). *J. gen. Physiol.*, **21**, 165.
WERTHEIM, T. (1894). *Z. Psychol. Physiol. Sinnesorg.*, **7**, 172.
WEYMOUTH, F. W., HINES, D. C., ACRES, L. H., RAAF, J. E., and WHEELER, M. C. (1928). *Amer. J. Ophthal.*, **11**, 947.

Brit. J. Ophthal. (1953) 37, 543.

PLASMA CELL MYELOMA OF THE ORBIT*

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THE manifestations of multiple myelomatosis are legion and in a small number of cases the orbit is involved. They present clinically as orbital space-occupying lesions and have been dealt with briefly elsewhere (Clarke, 1953), but no collective study of them is available, and the object of this paper is to review the problem and record two illustrative cases.

Myelomatosis is characterized by plasma cell tumours—myelomata or plasmacytomata—growing usually from the bone marrow but occasionally from extra-osseous tissues. Clinically the patient has generalized fatigue, loss of weight, anaemia, bone pains, and pathological fractures. Death occurs after an average survival of 2 years, in spite of any known treatment. *X* rays show typical osteolytic bone lesions, the urine frequently contains Bence Jones protein, the plasma globulin and blood sedimentation rate are increased, and a bone-marrow biopsy usually reveals an increase of plasma cells. This is the classical picture but there are several variants, ranging from a process that is fatal in a few months, to one in which the patient may survive for years. The "solitary" myeloma belongs to this latter group and was at one time thought to be a separate clinical entity. By the use of bone-marrow biopsy, extended follow-up, and detailed *post-mortem* studies, however, it has in almost all cases been proven to be but a stage in the generalized disease and almost invariably other evidence of myelomatosis may be found if it is looked for very carefully. It is maintained by some that a truly solitary lesion indistinguishable from the multiple tumour does sometimes occur (Cristopherson and Miller, 1950).

It is necessary to differentiate between the plasma cell myeloma of myelomatosis and the benign plasma cell tumour produced by chronic inflammation. Unfortunately, they are both termed "plasmacytoma" or "plasmocytoma", and there is considerable confusion in the literature concerning this important point. Their differentiation both clinically and histologically is not usually difficult but is obviously of great importance for prognosis and therapy. In this paper the term "plasmacytoma" has been reserved for the non-myelomatous, granuloma-type masses, and "plasma cell myeloma" or "myeloma" for the tumours associated with myelomatosis. Plasmacytomata (or, as they are sometimes called, plasmomata) grow from the conjunctiva, cornea, lids, and lacrimal gland or sac, as well as from the mucosa of the upper air passages, and are in no way related to multiple myeloma. Certain cases of orbital plasma cell tumours found in the liter-

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ature have been rejected as examples of myelomata because of their doubtful origins. Despite the opinions of the authors concerned, the cases of Parker (1937) and François, Kluyskens, and Rabaey (1949) have been excluded. There is some evidence that the orbital mass in each case was a true myeloma and not a granuloma such as Przyblyska (1924) described, but neither report includes information concerning full investigations, progress nor autopsy. Walsh (1947) could not be certain that the tumour in his patient was not a pseudotumour and the case therefore has not been included.

A special type of granuloma, the eosinophilic granuloma, has also led to confusion, and the case published by Krümmel (1950), in an article entitled "Eosinophiles Myelom (Plasmozytom)", was undoubtedly of this nature. Its occurrence in the orbit was described by Beller and Kornblueth (1951).

Incidence

The exact incidence of myeloma of the orbit is difficult to discover, for those dealing with orbital tumours are unlikely to see all cases of myelomatosis with this complication. Authors who have reviewed multiple myeloma do not mention it, and it is possible that in the past the myeloma has not been differentiated from kindred neoplasms. Thus, Birch-Hirschfeld (1930) in an exhaustive treatise on orbital tumours does not mention it directly, but includes an occasional case with other types of tumours. A measure of its rarity, however, can be obtained from the fact that Forrest (1949), reviewing 222 intra-orbital tumours, found only one " plasmocytoma " (myeloma), and that there were two myelomata in a series of 676 tumours described by Offret (1951). Pfeiffer (1941) had only one example among 200 cases of exophthalmos. The absence of myelomata is specifically noted by Godtfredsen (1947) when dealing with 78 cases of orbital tumour, representing 10,000 admissions to an ophthalmological clinic in 15 years.

Classification

Cases of myelomatosis with orbital involvement fall into two groups:

A. Primary myeloma of the orbit. The patient presents with ocular features, suggestive of an orbital tumour.

B. Secondary myeloma of the orbit. The patient has a para-orbital myeloma and eventually develops symptoms and signs of an orbital tumour due to orbital invasion.

Some of the cases in the literature, however, cannot be so grouped because of a paucity of information concerning them (Grosz, 1927; Verhoeff, 1939; Pfeiffer, 1941; Godtfredsen, 1944, Table XXX, Case 18; Forrest, 1949; Bichel, 1950, Case 6). It is possible, of course, that they were not all true plasma cell myelomata. The case of Elizabade, quoted by Scheinker (1938), could not be traced, and his statement (Scheinker, 1951) that the first case of myeloma had orbital involvement and was described by Burns (1824) is not correct; the case in question is the first example of chloroma.

A. Primary Myeloma of the Orbit.—The literature includes at least thirteen cases of orbital myeloma where the information given is sufficient to place them definitely in this group (Table). Only undoubted myelomata have been accepted and other evidence of myelomatosis was present in all of them.

TABLE

PRIMARY ORBITAL MYELOMATA

Author	Date	Sex	Age	Initial Features	Eye Affected	Duration		Treatment	Outcome
						Ocular Features alone	Total		
Quackenboss and Verhoeff ...	1906	M	58	Diplopia. Proptosis	Left	4 mths	8 mths	Operation	Death (no *post mortem*)
Mieremet	1915	F	57	Proptosis	Right	*c.* 5 mths	12 mths	Sodium cacodylate Salvarsan	Death (*post mortem*)
Morax	1919	M	42	Proptosis	Right	8 mths	*c.* 8 mths	Operation	Death (*post mortem*)
Branham and Lewis	1921	M	63	Pain; tumour in leg	Right	Not known	3 mths	None	Death (*post mortem*)
Greenough and others, Case 52	1921	M	48	Proptosis	Left	*c.* 1 yr	—	Irradiation	Alive (4½ yrs follow-up)
Holm (L. orbit)	1932	F	73	Tumour below eye	Left	14 mths	2 yrs	Operation. Irradiation	Death (*post mortem*)
Cruickshank	1937	M	30	Pain and proptosis	Left	13 mths	19 mths	Operation Radium	Death (no *post mortem*)
Flynn and Sailer	1941	M	68	Proptosis, ptosis, visual loss	Right	5 mths	7 mths	None	Death (*post mortem*)
Claisse and others, Case 8 ...	1949	M	31	"Ocular disorders" Orbital mass	Left	9 mths+	—	Diethylstilboestrol	Alive (9 mths follow-up)
Gerèb and Könyvès-Kolonics, Case 2	1950	F	56	Lumbago, general malaise, inflammation of eye	Left	—	Not known	None	Unknown
McEvoy	1950	F	80	Orbital mass	Right	3 mths	—	Operation. Irradiation	Alive (no follow-up)
Driessens and others	1951	F	45	Proptosis	Left	1 mth	Few mths	Stilbamidine	Death (no *post mortem*)
Offret	1951	F	57	Proptosis. Headaches	Right	6 mths	—	Operation. Irradiation	Alive (2½ yrs follow-up)
Clarke, Case 1	1953	M	67	Diplopia	Left	2 yrs	3½ yrs	Operation. Irradiation	Death (no *post mortem*)

To the cases shown in the Table, another may be added.

Case 1, male, 67 years.

One year of diplopia, 2 months of left ptosis and proptosis. Left supraciliary mass and X-rays showed osteolytic lesions in this and other regions. Partial removal of left orbito-frontal tumour (verified as myeloma) and radiation therapy given, but generalisation and local recurrence occurred. Death. Total survival 3¼ years. No autopsy.

This patient, a butcher by trade, was admitted to the Radcliffe Infirmary, Oxford, on May 18, 1949, under the care of the late Sir Hugh Cairns. One year before admission he noticed double vision which was constantly present and most marked when looking downwards. For 2 months there had been progressive drooping of the left upper lid and slight protrusion of the eye.

Examination.—General condition good. Slight proptosis of the left eye, the globe being pushed downwards and slightly laterally. In the left supraciliary region there was a firm, non-tender mass, and a similar lesion was palpable in the right occipital region.

Visual acuity right eye J1, left eye J2 (uncorrected).

Optic fundi, visual fields, and pupils all normal. Upward movement and adduction of left eye slightly limited, with production of diplopia in all directions.

Central nervous system and other systems normal.

Investigations

X rays of skull showed a large area of bone destruction in the left frontal region extending to the orbit, and similar but much smaller areas elsewhere (Fig. 1).

Urine, no Bence Jones proteinuria.

FIG. 1.—Case 1, *x* ray of skull showing large left orbito-frontal myeloma and smaller ones elsewhere.

Operation (Mr. J. B. Curtis) May 26, 1949.—Soft vascular tumour found in left supraciliary region; much of the orbital roof on this side had been destroyed; tumour tissue in the orbit. Only partial excision was possible.

Histology.—The material removed had the microscopical appearance of a myeloma (Fig. 2).

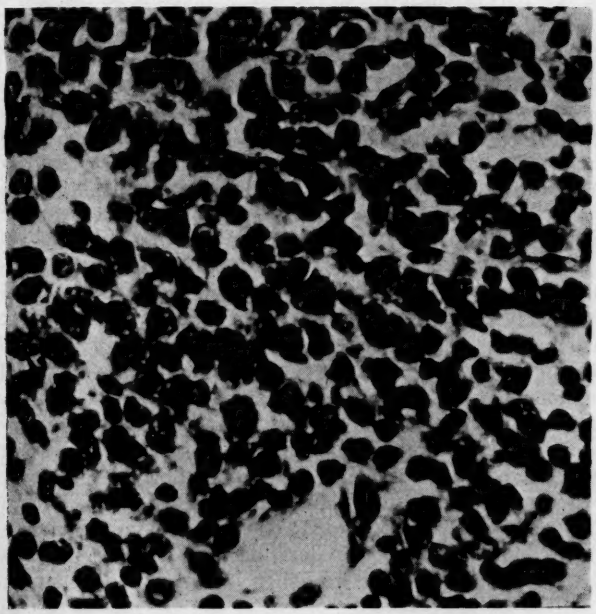

FIG. 2.—Case 1, photomicrograph of myeloma. The principal elements are plasma cells. (×580)

Progress.—The patient made a good post-operative recovery and was given three courses of deep *x*-ray therapy directed to the left orbital region. The proptosis and diplopia disappeared and he was discharged on June 3, 1949. A year later, he was found to have a myelomatous deposit in the 6th thoracic vertebral body, and 6 months after this noticed the return of proptosis, ptosis, and diplopia. He was given another course of radiation therapy but after 6 months his condition had deteriorated further. He now had evidence of left cerebral hemisphere compression and he died on August 8, 1951, 3¼ years after the onset of the disease. It was not possible to carry out an autopsy.

Comment.—This was a typical case of multiple myeloma presenting with ocular features due to an orbital myeloma that had presumably spread to the frontal bone. Its exact site of origin cannot be determined but may have been the contents or roof of the orbit. Partial removal and irradiation produced only temporary improvement and the classical course of the disease was observed.

Pathology.—The myeloma in these cases apparently grows from the orbital contents or walls, but at a late state of its development it is usually impossible to identify the structure from which it arose. Morax (1926) thought that this was invariably the roof of the orbit, but Flynn and Sailer (1941) noted that in their case the tumour was limited to the contents of the orbit and that its confines were intact. In addition, no *x*-ray evidence of bony erosion could be found in the cases of Claisse, Bonduelle, and Lavergne (1949, Case 8), McEvoy (1950), and Offret (1951). The primary myeloma may thus be a product of the orbital contents and therefore of extra-osseous origin; unfortunately there seems to be no information con-

cerning the actual tissue that is initially responsible. Frequently the tumour eventually destroys the surrounding bone (Mieremet, 1915; Morax, 1919; Holm, 1932; Case 1 above), and it may extend through the roof and compress the under surface of the frontal lobe of the brain as in the cases of Morax (1919), Branham and Lewis (1921), Holm (1932), and Case 1, above.

Clinical Picture.—In all but one of the fourteen cases, symptoms referable to the eyes were either the earliest, or amongst the earliest, manifestations of the disease. The commonest complaint was that of progressive protrusion of an eye, the globe being displaced in any direction. Whereas malignant orbital neoplasms usually present with ocular immobility, proptosis is much commoner as an initial symptom in these cases of plasma cell myeloma. Occasionally the tumour can be palpated within the orbit and is of a firm consistency but never tender. Reduction of the eye is rarely possible and marked pulsation does not occur. The next most common feature is impairment of vision which varies from total blindness to only slight involvement; the mechanism of its production has not been investigated. Diplopia due to restricted ocular movements is less frequent and papilloedema and pupillary changes have been only rarely mentioned. Unfortunately clinical details in several reports are scanty; no accounts of visual fields nor detailed fundus examinations are available. Unlike other malignant orbital neoplasms, and plasma cell myelomata elsewhere, pain is rarely experienced. It is important to note that in twelve cases these clinical features were the initial manifestations of multiple myelomatosis, being present alone for several months (1 to 24, average 8). When other evidence of myeloma appeared, the process usually proceeded to the rapidly fatal termination that is to be expected in this disease. The shortest duration was 3 months (Branham and Lewis, 1921) and the longest 4½ years (Greenough, Simmons, and Harmer, 1921, Case 52). The latter case is an example of one of the variants of myelomatosis where the course of the disease is slower than in the classical type. If this case be excluded, the average survival of the patients with primary orbital myelomas (eight cases) was 15 months. Four were still alive when reported, the longest follow-up being that of Greenough and others (1921).

Diagnosis.—A myeloma should be considered if an orbital tumour produces bony destruction. The investigations mentioned above should always be carried out in order to find evidence elsewhere of myelomatosis. Biopsy clinches the diagnosis.

Treatment.—There is no cure for multiple myelomatosis, and only palliative measures are available. Three main methods of therapy exist: histiotoxic drugs, irradiation, and surgery. Of the drugs, stilbamidine, nitrogen mustard, and radio-active phosphorus have given disappointing results, although the former frequently relieves pain and the latter may produce subjective improvement. Although it is too early to evaluate them adequately, no striking effects have been noted either with ACTH or cortisone. Experiences with urethane have been a little more encouraging (Luttgens and Bayrd, 1951), but toxic manifestations are common. Radiation therapy seems to have definite beneficial effects upon local lesions but it is doubtful if it influences the generalized disease. Surgery has a limited application and its scope is dependent upon the location and size of the myeloma.

Of the nine patients with primary orbital myelomata (Table) that are known to have died, two had no treatment, two had medical therapy with no effect upon the course of the disease, and five were operated upon but only partial removal of the

tumours was possible and recurrence occurred in each instance despite the addition of radiation therapy in three. The surviving patients were given irradiation, either alone or supplemented with surgery. The best form of therapy, however, is probably a judicious combination of the three modes. Only partial surgical removal of an orbital myeloma would in most cases be possible, but this would be followed by deep *x*-ray irradiation and a course of urethane. All other measures aimed at decreasing the patient's discomfort should, of course, be employed. Active treatment of the orbital lesion would only be resorted to if it alone was producing symptoms or the disease was only slowly progressive and the patient's general condition and expectation of life warranted it. Nevertheless, one gains the impression that the eventual outcome is dependent not upon the therapeutic agents employed but upon the predetermined course of the disease as a whole.

B. SECONDARY MYELOMA OF THE ORBIT.—In these cases, the primary focus is in the para-orbital structures—cranial bones, paranasal air sinuses, nose, or naso-pharynx—and the orbit is encroached upon secondarily. Again, if the case is seen at a late stage, it may be impossible to say which structure was affected first, but the initial features of the illness are usually suggestive. Myelomata of tissues adjacent to the orbit will be dealt with in turn.

Cranial bones.—The bones of the cranium are said to be involved in over 70 per cent of cases of myelomatosis (Bayrd and Heck, 1947) and it is therefore not surprising that occasionally a myeloma is found to extend into the orbit. Lesions in the temporal region, which entered the orbit to produce ocular symptoms and signs, have been described by Rustizky (1873), Ribbert (1904), de Harven, Murdoch, and Cahen (1927), Ferrand (1951), and Pages, Betoulières, and Cazaban (1952). Similarly, frontal bone myelomata invading the orbit occurred in the cases of Lecène (1919), Dick (1904), Lapointe (1929), Ibañez Puiggari, Balado, and Gaviña Alvarado (1930), Geréb and Könyves-Kolonics (1950, Case 1); and probably those of Duc (1937) and Krainin, D'Angio, and Smelin (1949), also had orbital extensions. In Case 1 above, the events were reversed and the frontal bone was invaded after the orbit. The end result, however, is the same and the only method of differentiating the two groups is by the clinical information. The following case illustrates this type of orbital involvement.

Case 2,* female, 60 years.

Headache for 9 months following left frontal injury. Left frontal, osteolytic tumour with left ptosis and proptosis for 3–4 months. Biopsy revealed myeloma. Bence Jones proteinuria. Partial removal with development of coma and right hemiplegia, not influenced by further decompression. Death. Total survival about 9 months. Autopsy. Myeloma involved sinuses and orbital roof.

A housewife aged 60 years was admitted to the London Hospital on March 24, 1938, under the care of the late Sir Hugh Cairns. Nine months before admission she fell and struck the left side of her head but did not lose consciousness. Thereafter she suffered headaches which were mainly left frontal. For 3–4 months, there had been a swelling of the left forehead, the left eye was slightly more prominent and the upper lid was drooping. Recently she had been less alert mentally but had no other symptoms.

Examination.—A slightly obese, cheerful woman, in no apparent distress. A mass 11 cm. in diameter occupied the left frontal bone. Its elevation above the skin surface was slight but it

*This case is Case 4 of Clarke (1953).

FIG. 3.—Case 2, myeloma of left frontal bone can be seen as well as ocular features.

extended down to involve the supra-orbital region and upper orbit. It was slightly tender, fluctuant, and a distinct systolic bruit, which could be obliterated by pressure on the ipsilateral carotid artery, was heard over it. The irregular edge of a cranial defect could be felt beneath. There was slight proptosis and ptosis on the left and a fullness above the eye (Fig. 3).

Visual acuity, both eyes 6/18 and J1 (corrected).

Optic discs and fields normal. Left pupil slightly smaller than the right but had normal reactions; upward and lateral movements of left eye restricted.

Central nervous system and other systems normal.

Investigations

X rays of skull showed extensive destruction of left frontal region extending to left orbit (Fig. 4); chest normal; long bones normal.

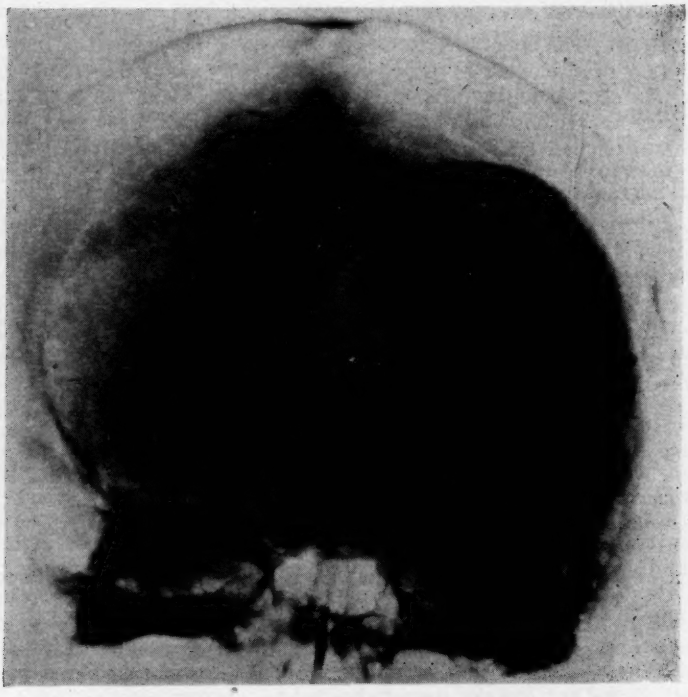

FIG. 4.—Case 2, *x* ray of skull showing large fronto-orbital myeloma.

Cerebrospinal fluid pressure 140 mm.; cells 1; protein 25 mgm. per cent; Lange no change; Wassermann reaction negative.

Blood haemoglobin 94 per cent; white cells 8,960 (differential count normal).

Urine: Bence Jones protein present.

Biopsy (30.3.38) Mr. J. B. Pennybacker. Tissue removed from skull tumour reported by Professor D. S. Russell as being diagnostic of a myeloma (Fig. 5, opposite).

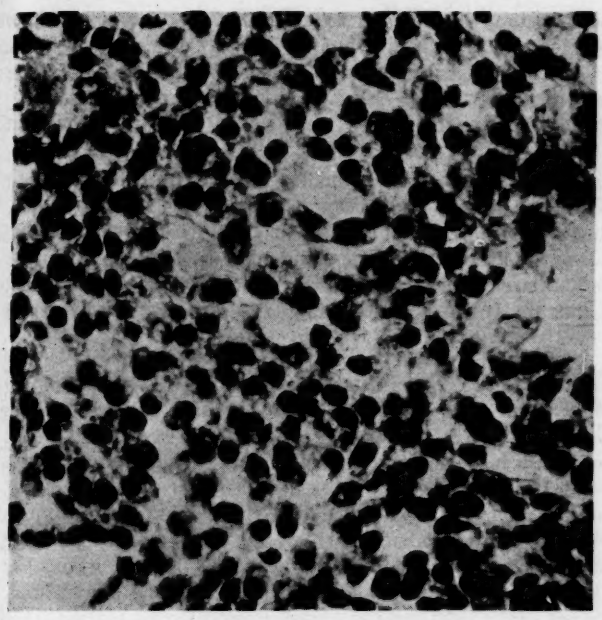

FIG. 5.—Case 2, photomicrograph of frontal bone myeloma. The tumour consists mainly of plasma cells. (×580)

First Operation (5.4.38) Sir Hugh Cairns and Mr. J. B. Pennybacker. The tumour, although a product of the bone, was firmly attached to the dura mater which was intact except for two areas at the centre of the tumour where the myelomatous tissue had extended through it. An attempt was made to remove the tumour, but partly because of its vascularity (ligation of the ipsilateral common carotid artery did not help) and partly because of its adherence to the dura, this was only partially successful.

Progress.—The following day the patient was comatose and had a right hemiplegia, and as there was no improvement a second operation was carried out on April 7, 1938. The left frontal lobe was very oedematous and a portion of it was removed. There was some temporary improvement, but she did not regain consciousness and died 2 days later.

Autopsy (J.R.C.).—The remnants of the myeloma were found and it was seen that tumour tissue had invaded the left frontal, left ethmoidal, and right frontal sinuses, and that there was a defect in the roof of the orbit, with growth on the surface of the orbital fascia displacing the contents. The bone marrow was normal to macroscopical examination in the sternum, vertebrae, one humerus, ribs, and other bones. No other abnormal features were detected.

Comment.—The myeloma in this case had grown from the frontal bone to involve the orbit secondarily, and although it was single, the presence of Bence Jones proteinuria indicated a more widespread process. Nevertheless it was felt that surgical intervention was justified, but the difficult operation illustrates the hazards of attempting complete excision of these neoplasms. As in the cases of Morax (1919) and Fuerster and Zuckerman (1950), there was a close relationship with trauma; Geschickter and Copeland (1928) found a definite correlation in 20 per cent. of 425 cases of multiple myeloma.

Pathology.—All these cases had evidence of myelomatosis elsewhere and the frontal or temporal tumour was usually noticed before the orbit was invaded. The

ocular features produced thereby were similar to those already considered in the preceding group. The outcome was much the same as in any other case of multiple myeloma, death being invariably due to generalization of the disease, which, in fact, was frequently already present when the cranial tumour appeared. Treatment seemed to have little or no effect upon these patients, the methods used being the same as in the previous group.

Myelomata of the bone of the skull base extending forward into the orbit and behaving like space-occupying lesions have been described by Rustizky (1873), Hoffmann (1904), Heilmann (1928), Seemann (1930), Piney and Riach (1931, Case 1), and Christophe and Divry (1940, Case 1). The clinical picture is usually complex because cranial nerves and structures other than the orbit are involved, but in at least one of them (Seemann, 1930) the initial diagnosis was that of malignant orbital tumour.

Mucous Membrane.—One of the commonest extra-osseous sites for myelomata is the mucous membrane of the upper respiratory pathways, although here as with the ocular structures there has been considerable confusion caused by authors failing to differentiate between plasma cell myelomata and plasma cell granulomata (plasmacytomata). Ringertz (1938) surveyed 391 neoplasms arising from nasal, paranasal, and pharyngeal regions, and found eleven plasma cell tumours, although it is possible that some were not myelomatous. Nevertheless, although distortion from a distance was common, none is recorded as having invaded the orbit. The patient reported by Hajek (1926) had a myeloma of the frontal and ethmoid sinus, and this had also occurred in the right orbit of a patient reported by Holm (1932). Fuerste and Zuckerman (1950) described a case with a myeloma of the antrum which grew to an enormous size with orbital invasion and hideous facial disfiguration. The myeloma grew from nasal or sinus cavities in the cases of Pallestrini (1927), Saarni (1933), and Tokumitsu and Takigawa (1936, Case 2); in the last, there was bilateral orbital involvement, a feature which was present also in the patients of Holm (1932) and Dick (1904). A case described by Greenfield (1948) is interesting, for a naso-pharyngeal myeloma is said to have extended to the orbit but, as no radiological or pathological proof is presented, it is possible that there was more than one myeloma present. The first indications of cranial involvement in these cases were symptoms referable to the nose, and nasal obstruction predominated; it was thus possible to detect the site of origin of the myeloma. As with the cranial bone myelomata, the ocular features developed later but were in no way distinctive except that as with any other tumour originating from the nose or sinus, the globe was displaced forwards and laterally. The local spread of myelomatous tissue was usually extensive but, apart from the case of Pallestrini (1927) where meningitis was the terminal event, death was due to the generalized disease as much as the cranial myeloma. As in the other cases of orbital myeloma, treatment is not very helpful, especially as the lesions are often deep as well as invasive. The measures described already are adopted.

Summary

The orbit is occasionally involved in multiple myelomatosis, and symptoms and signs of an orbital space-occupying lesion produced by a plasma cell

myeloma may be the first manifestation of this disease. The orbital myelomata are of two types:

A. PRIMARY.—The clinical picture is that of an orbital tumour and the myeloma grows from the contents or confines of the orbit.

B. SECONDARY.—The patient has a myeloma of adjacent bone or nasal or sinus cavities and later develops features of orbital invasion.

An example of each variety is described and pathological, clinical and therapeutic aspects are discussed.

My thanks are due to Mr. J. B. Pennybacker for allowing me to publish the case records of the two patients, and also for his valuable advice and criticism.

REFERENCES

BAYRD, E. D., and HECK, F. J. (1947). *J. Amer. med. Ass.*, **133**, 147.
BELLER, A. J., and KORNBLUETH, W. (1951). *British Journal of Ophthalmology*, **35**, 220.
BICHEL, J. (1950). *Ugeskr. Laeg.*, **112**, 790.
BIRCH-HIRSCHFELD, A. (1930). "Die Krankheiten der Orbita." Chap. 13 in "Handbuch der gesamten Augenheilkunde", ed. Graefe and Saemisch, vol. 9 (part 1). Springer, Berlin.
BRANHAM, V. C., and LEWIS, N. D. C. (1921). *Med. Rec. N.Y.*, **99**, 169.
BURNS, A. (1824). "Observations on the Surgical Anatomy of the Head and Neck", 2nd ed., pp. 386–392. Wardlaw and Cunninghame, Glasgow.
CHRISTOPHE, L., and DIVRY, P. (1940). *J. belge Neurol. Psychiat.*, **40**, 279.
CHRISTOPHERSON, W. M., and MILLER, A. J. (1950). *Cancer*, **3**, 240.
CLAISSE, R., BONDUELLE, M., and LAVERGNE, G. H. (1949). *Sem. Hôp. Paris*, **25**, 249.
CLARKE, E. "Cranial and Intracranial Myelomata". (To be published).
CRUICKSHANK, M. M. (1937). *Brit. J. Surg.*, **24**, 615.
DICK, G. F. (1904). *Trans. Chicago path. Soc.*, **6**, 168.
DRIESSENS, FRANÇOIS, P., WOILLEZ, and VERDICKT (1951). *Bull. Soc. Ophtal. franç.*, p. 26.
DUC, C. (1937). *Rass. ital. Ottalm.*, **6**, 719.
FERRAND, J. (1951). *Bull. méd. Afr. occid. franç.*, **8**, 43.
FLYNN, J., and SAILER, S. (1941). *Ohio St. med. J.*, **37**, 771.
FORREST, A. W. (1949). *Arch. Ophthal., Chicago*, **41**, 198.
FRANÇOIS, J., KLUYSKENS, J., and RABAEY, M. (1949). *Ann. Oculist., Paris*, **182**, 729.
FUERSTE, F., and ZUCKERMAN, S. S .(1950). *Arch. Otolaryng., Chicago*, **51**, 608.
GERÉB, T., and KŐNYVES-KOLONICS, L. (1950). *Orv. Hetil.*, **91**, 282.
GESCHICKTER, C. F., and COPELAND, M. M. (1928). *Arch. Surg., Chicago*, **16**, 807.
GODTFREDSEN, E. (1944). *Acta oto.-laryng., Stockh., Suppl.* 59.
——— (1947). *Acta ophthal., Kbh.*, **25**, 279.
GREENFIELD, M. M. (1948). *Radiology*, **50**, 661.
GREENOUGH, R. B., SIMMONS, C. C., and HARMER, T. W. (1921). *J. orthop. Surg.*, **3**, 602.
GRÓSZ, E. VON. (1927). *Z. Augenheilk.*, **63**, 309.
HAJEK, M. (1926). *Beitr. Anat. etc. Ohr.*, **23**, 465.
DE HARVEN, MURDOCH, and CAHEN (1927). *Bull. Ass. franç. Cancer*, **16**, 287.
HEILMANN, P. (1928). *Beitr. path. Anat.*, **80**, 652.
HOFFMANN, R. (1904). *Ibid.*, **35**, 317.
HOLM, E. (1932). *Acta ophthal., Kbh.*, **10**, 334.
IBÁÑEZ PUIGGARI, M., BALADO, M., and GAVIÑA ALVORADA, E. (1930). *Sem. med., B. Aires*, **1**, 781.
KRAININ, P., D'ANGIO, C. J., and SMELIN, A. (1949). *Arch. intern. Med.*, **84**, 976.
KRÜMMEL H. (1950). *Klin. Mbl. Augenheilk.*, **117**, 620.
LECÈNE, P. (1919). *Ann. Oculist., Paris*, **156**, 249.
LANGDON, H. M. (1939). *Trans. Amer. ophthal. Soc.*, **37**, 223.
LAPOINTE, A. (1929). *Bull. Soc. nat. Chir.*, **55**, 456.
LUTTGENS, W. F., and BAYRD, E. D. (1951). *J. Amer. med. Ass.*, **147**, 824.
MCEVOY, J. J. (1950). *Arch. Ophthal., Chicago*, **44**, 163.
MIEREMET, C. W. G. (1915). *Virchows Arch.*, **219**, 1.
MORAX, V. (1919). *Ann. Oculist., Paris*, **156**, 256.
——— (1926). "Cancer de l'appareil visuel", p. 424. Doin, Paris.
OFFRET, G. (1951). "Les tumeurs primitives de l'orbite", p. 268. Masson, Paris.
PAGES, P., BETOULIÈRES, P., and CAZABAN, R. (1952). *Ann. Oculist., Paris*, **185**, 632.
PALLESTRINI, E. (1927). *Arch. Sci. med.*, **51**, 175.
PARKER, S. T. (1937). *Proc. roy Soc. Med.*, **31**, 130.

PFEIFFER, R. L. (1941). *Trans. Amer. ophthal. Soc.*, **39**, 492.
PINEY, A., and RIACH, J. S. (1931). *Folia haemat., Lpz.*, **46**, 37.
PRZYBYLSKA, J. (1924). *Ann. Oculist., Paris*, **161**, 198.
QUACKENBOSS, A., and VERHOEFF, F. H. (1906). *J. med. Res.*, **15**, 261.
RIBBERT, H. (1904). *Zbl. allg. Path. path. Anat.*, **15**, 337.
RINGERTZ, N. (1938). *Acta oto-laryng., Stockh.*, Suppl. 27.
RUSTIZKY, J. VON (1873). *Dtsch. Z. Chir.*, **3**, 162.
SAARNI, E. (1933). *Arch. Ohr.-, Nas.-, u. Kehlk Heilk.*, **136**, 54.
SEEMANN, G. (1930). *Zbl. allg. Path. path. Anat.*, **48**, 212.
SCHEINKER, I. (1938). *Dtsch. Z. Nervenheilk.*, **147**, 247.
——— (1951). " Medical Neuropathology ", p. 252. Thomas, Springfield, Ill.
TOKUMITSU, K., and TAKIGAWA, K. (1936). *Gann*, **30**, 387.
VERHOEFF, F. H. (1939). In discussion of paper by Langdon (1939).
WALSH, F. B. (1947). " Clinical Neuro-Ophthalmology ", p. 1115. Williams and Wilkins, Baltimore.

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CHANGES IN THE REFRACTIVE POWER OF THE CORNEA DURING GROWTH*

OBSERVATIONS ON THE RABBIT

BY

ARNOLD SORSBY AND MICHAEL SHERIDAN†

London

MANY studies have been made of the changes of refraction of the eye during infancy and childhood, but little is known of the changes in the individual components of total refraction. Such changes must be of considerable magnitude to compensate for the axial elongation of the globe during growth, for the refraction of the adult eye with its longer axis differs but little from that seen in early life. Axial elongation during growth, considered by itself, should produce a change of the order of some 20 or 30 D., for the eye of the newborn child is some 16 mm. long, whereas that of the adult is 23 or 24 mm. That no such marked change in refraction occurs is obvious from daily experience. Axial elongation must therefore be compensated for by a reduction in the refractive power of the cornea-lens system, but actual evidence of this process is lacking.

The following observations, carried out on the rabbit, aimed at determining the changes in the refraction of the cornea over some 6 months from the 4th week of life (when the rabbit could be safely handled). These changes were related to observations on the refraction of the eye as a whole.

The cornea of the adult rabbit—as determined in 24 animals—shows a radius of curvature ranging between 7.5 and 8.25 mm., the common values being 7.7 to 8.0 mm. The common refractive power of the cornea is therefore about 42 to 44 D. In attempting to measure the radius of curvature of the baby rabbit at 4 weeks it was found that no readings could be recorded on the Javal-Schiötz keratometer (Haag-Streit), which is calibrated to an upper limit of 5.5 mm. (corresponding to about 61.5 D). It was only when the rabbit was 6 weeks old that a reading could be obtained. The Table shows the keratometer reading in mm. of the radius of curvature in four litter-mates, taken at weekly intervals for about 2 months, and at longer intervals subsequently. In the Figure the readings recorded in dioptres are shown against the refraction of the eye as determined by retinoscopy under atropine cycloplegia at the same time. It will be seen that in the rabbit, as in man, there is relatively little change in refraction of the eye during growth—and this in spite of the fact that over the 6 months of observation the refraction of the cornea declined from a value of over 60 D. to well below 50 D., and is

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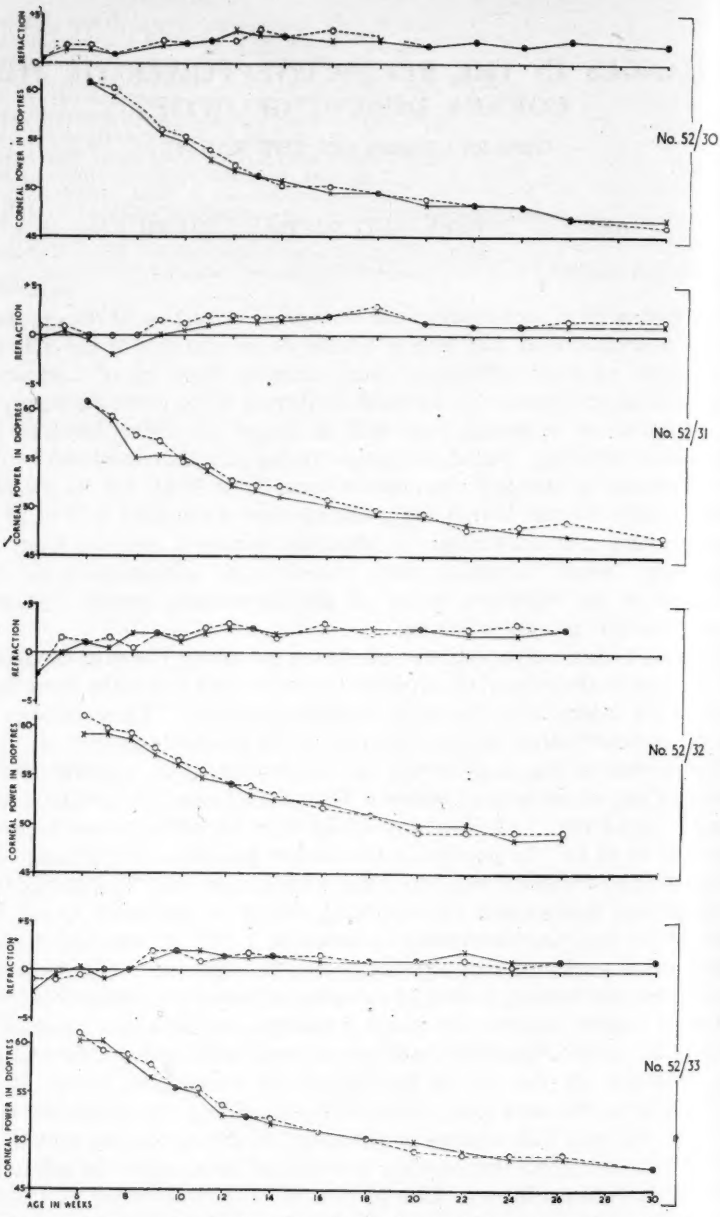

FIGURE.—Four graphs showing the refractive power of the cornea in each eye during the period 6 to 30 weeks in four rabbit litter-mates, set against refraction of the eye under atropine cycloplegia during the period 4 to 30 weeks.
Full line=right eye; broken line=left eye.
Corneal power and refraction of the eye both shown in vertical meridian only.

TABLE

RADIUS OF CURVATURE OF CORNEA (mm.) IN FOUR RABBIT LITTER-MATES

Rabbit Number		52/30♂				52/31♂				52/32♀				52/33♀			
Eye		Right		Left		Right		Left		Right		Left		Right		Left	
Meridian ..		V	H	V	H	V	H	V	H	V	H	V	H	V	H	V	H
Age in Weeks	4	Beyond the limit of the keratometer scale															
	5																
	6	5·55	5·55	5·55	5·57	5·55	5·55	5·55	5·55	5·68	5·63	5·53	5·58	5·58	5·63	5·53	5·60
	7	5·71	5·59	5·62	5·72	5·73	5·68	5·70	5·73	5·68	5·65	5·65	5·68	5·60	5·69	5·70	5·78
	8	—	—	—	—	6·15	5·99	5·88	5·94	5·73	5·70	5·69	5·76	5·78	5·77	5·74	5·74
	9	6·08	6·05	6·02	6·10	6·10	5·99	5·96	6·08	5·91	5·95	5·83	5·95	5·98	5·99	5·85	5·93
	10	6·15	6·20	6·12	6·25	6·15	6·00	6·17	6·10	6·02	5·99	5·98	6·05	6·08	6·08	6·08	6·17
	11	6·41	6·32	6·30	6·42	6·22	6·22	6·28	6·50	6·17	6·08	6·07	6·18	6·12	6·09	6·10	6·20
	12	6·52	6·55	6·45	6·51	6·44	6·42	6·38	6·41	6·22	6·24	6·22	6·28	6·40	6·40	6·30	6·35
	13	6·60	6·67	6·58	6·68	6·52	6·46	6·45	6·51	6·37	6·42	6·27	6·32	6·43	6·40	6·43	6·42
	14	6·62	6·60	6·65	6·81	6·60	6·49	6·45	6·66	6·40	6·36	6·38	6·36	6·51	6·45	6·48	6·50
	16	6·80	6·72	6·75	6·88	6·70	6·70	6·65	6·70	6·48	6·51	6·52	6·48	6·62	6·62	6·62	6·75
	18	6·82	6·80	6·82	6·89	6·88	6·78	6·81	6·78	6·62	6·63	6·62	6·70	6·70	6·78	6·71	6·78
	20	7·00	6·73	6·95	7·18	6·92	6·88	6·88	6·98	6·75	6·72	6·84	6·78	6·75	6·78	6·89	6·88
	22	7·00	7·00	7·00	7·08	7·01	6·92	7·05	7·02	6·75	6·78	6·84	6·73	6·95	6·90	6·89	6·95
	24	7·05	7·10	7·05	7·10	7·11	7·03	7·06	7·08	6·95	6·83	6·84	6·88	7·02	6·96	6·98	7·00
	26	7·19	7·10	7·20	7·19	7·15	7·00	6·95	7·19	6·91	6·94	6·85	6·91	7·02	7·05	6·98	7·00
	30	7·21	7·12	7·30	7·28	7·24	7·13	7·18	7·25	—	—	—	—	7.14	7·14	7·14	7·20

V = Vertical H = Horizontal

still falling: the adult value has not yet been reached, though the rabbits are almost fully grown. In these observations no attempt was made to assess changes in the refraction of the lens or in the depth of the anterior chamber.

Changes in the baby rabbit are, of course, not strictly applicable to man, for the baby rabbit is more immature than the human infant. The valid observation is that during the growth of the rabbit eye—and this was obvious and considerable, though not actually measured—the refraction as determined by retinoscopy changed but little, whilst the decline in the refractive power of the cornea was marked. Some 15 D. of total refraction were lost by changes in the cornea of these baby rabbits during the time when the axis of the eye became longer and therefore tended to produce myopia. " Growth myopia " was fully compensated.

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CURARE AND CURARE-LIKE PRODUCTS IN CATARACT SURGERY*

BY

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AFTER the presentation of the previous report (Agarwal and Mathur, 1952) on the use of d-tubocurarine chloride in muscular relaxation during cataract operations, it was decided to assess the relative merits and demerits of curare and curare-like products. A further 75 cases were studied, and both local and general effects were noted with the following products, each in 25 cases:

(1) d-Tubocurarine chloride.
(2) Dimethyl tubocurarine iodide.
(3) Gallamine triethiodide.

The doses were calculated on the following basis:

(1) 1 mg. d-tubocurarine chloride—7 units.
(2) 1 mg. dimethyl tubocurarine iodide—21 units.
(3) 16 mg. gallamine triethiodide—21 units.

The curare and curare-like products were assayed by the "head-drop cross-over test" in rabbits.

PHARMACOLOGY

Bernard (1865) reported that curare causes paralysis by its action on the myoneural junction of striated muscles by nullifying the action of acetyl choline on individual muscle fibres. It has no action on sensory nerves nor on the central nervous system. In low doses the general muscle tone is quietened, a mild paresis follows, and finally complete paralysis occurs, indicating that the interference at the nerve ending is purely quantitative. The curare has its full manifest effect in about 5 minutes and the effect lasts for about 30 minutes. It acts by intravenous administration. d-Tubocurarine chloride in larger doses affects the muscles supplied by the autonomic nervous system by the same mechanism as that by which it affects the striated muscles. Gallamine triethiodide, even in large doses, has little action on the autonomic nervous system and does not give rise to histaminoid reactions. Depierre (1947) and Hingson and others (1949) feel that dimethyl tubocurarine iodide causes no respiratory embarrassment even in large doses.

The action of all these compounds is completely reversed by anticholinesterase agents.

* Received for publication April 9, 1953.

Clinical Investigations

The indications and contraindications of these drugs have already been listed in a previous report (Agarwal and Mathur, 1952).

Material.—75 cases of cataract were given one of these drugs and the effects were noted. No selection of cases was done except in patients in whom curare products were contraindicated.

Method.—Routine preparation was carried out. Luminal was used as a premedicant (1 gr. at bed time the night before and 1 gr. an hour before the operation). Atropine 1/100 gr. was given 30 minutes before operation. Topical anaesthesia was given by 2 per cent. anethaine four times every 5 minutes. Curare was then administered by the intravenous route into a vein in the cubital fossa. Oxygen, adrenaline, eserine, prostigmine, laryngoscope, and intratracheal intubation requirements were kept ready for emergencies.

Dose.—20 units curare or its equivalent were given in one minute, then 10 units every half minute until paresis began to appear; the administration was continued till the desired effect was obtained (Table I).

TABLE I. DOSAGE

Drug Employed	Dose for Ptosis			Total Dose			No. of cases tried
	Min.	Max.	Average	Min.	Max.	Average	
d-Tubocurarine chloride ...	20	50	32	35	70	50	25
Gallamine triethiodide ...	20	37	26	26	47	39	25
Dimethyl tubocurarine iodide...	12	32	22	20	42	33	25

Observations (Tables II and III)

(*i*) Blood pressure, depth and rate of respiration, pulse rate, and pupillary reactions.
(*ii*) Tension, blinking reflex, ptosis, and ocular motility.
(*iii*) General muscular tone and relaxation.
(*iv*) Time after which maximum effects were obtained and for which effects lasted.

TABLE II. TIME OBSERVATIONS

Drug Employed	Average time for action to develop (min.)	Time for which effect lasts (min.)
d-Tubocurarine chloride ...	4½	30
Gallamine triethiodide	3	22
Dimethyl tubocurarine iodide ...	3	25

TABLE III. BLINKING REFLEX AND TENSION

Drug Employed	Blinking Reflex (per min.)	Tension Fall (mm. Hg)		
		Min.	Max.	Average
d-Tubocurarine chloride ...	Reduced to 4 on an average	2	7	6
Gallamine triethiodide	Reduced to 2	0	10	3
Dimethyl tubocurarine iodide ...	Reduced to 8 on an average	1	10	5

The total dose did not show any relationship to weight, age, or sex of patient; this is in agreement with Drucker and others (1951) and Agarwal and Mathur (1952) and contrary to Roche (1950) who advocated ½ unit per lb. bodyweight.

Other Effects.—These patients showed no ocular prominence nor any evidence of sympathetic paralysis. There was no change in the pupillary size. The ocular motility was reduced to command movements. The findings were constant for all the three drugs, in agreement with Drucker and others (1951) and Agarwal and Mathur (1952).

General Effects.—With all these drugs the patients did not exhibit any change in cerebral state of consciousness. There was no cerebral depression. With d-tubocurarine chloride a few cases showed increased respiration, though in most of them the rate was unchanged. The depth of respiration showed no significant change. Similar findings were obtained by dimethyl tubocurarine iodide. The respiration with this drug was more regular and easy as compared with d-tubocurarine chloride. With gallamine triethiodide in many cases there was an increase in the respiratory rate and the depth of respiration showed a decrease, indicating that there was a lessening of the vital capacity. With d-tubocurarine chloride and dimethyl tubocurarine iodide the changes in pulse and in blood pressure were insignificant, whereas with gallamine triethiodide there was an increase both in systolic and diastolic blood pressure as well as in pulse rate, indicating that there was some effect on the autonomic nervous system in the form of sympathetic stimulation. The general muscular relaxation was most pronounced by dimethyl tubocurarine iodide and least by gallamine triethiodide.

Discussion

Curare and curare-like products act by relaxation of skeletal muscles and have no anaesthetic properties. These drugs are best used by intravenous injection. Their topical or local use is not recommended. In the dosage as ordinarily used in ophthalmic surgery they have no autonomic action, with the exception of gallamine triethiodide. The action of gallamine triethiodide on the autonomic nervous system is within safe limits, but the drug requires to be used with greater caution. From this point of view, dimethyl tubocurarine iodide appears to be safest.

The dosage employed varies from 20 to 70 units. On an average smaller doses of dimethyl tubocurarine iodide are required. There is a small fall in intra-ocular pressure with all three drugs in cataract cases.

Kirby (1950), Roche (1950), Clark (1949), Cordes and Mullen (1951), and Agarwal and Mathur (1952) have advocated their cautious use in cataract surgery.

Summary

(1) The technique of administration is described.

(2) The action of three drugs is compared (d-tubocurarine chloride, gallamine triethiodide, and dimethyl tubocurarine iodide).

(3) The muscular relaxation, allaying of apprehension, and limitation of ocular movements caused by the curare-like drugs enable them to be used with safety in cataract extraction without vitreous prolapse.

(4) Dimethyl tubocurarine iodide is the safest of the three.

(5) The use of curare as an adjuvant in cataract surgery is confirmed.

We are grateful to Abbotts Laboratories, Chicago, U.S.A., and Burroughs, Wellcome, England, for the supply of d-tubocurarine chloride, to the Eli Lilly Co., Indiana, U.S.A., for the supply of dimethyl tubocurarine iodide, and to May and Baker, England, for the gallamine triethiodide.

REFERENCES

AGARWAL, L. P., and MATHUR, S. P. (1952). *British Journal of Ophthalmology*, **36**, 603.
BERNARD, C. (1865). *Bull. gén. Thér., Paris*, **69**, 23.
CLARK, W. B. (1949). *Watson Gailey Eye Foundation Quarterly*, **1**, 34.
CORDES, F. C., and MULLEN, R. S. (1951). *Amer. J. Ophthal.*, **34**, 557.
DEPIERRE, F. (1947). *C.R. Acad. Sci.*, **225**, 956.
DRUCKER, A. P., SADOVE, M. S., and UNNA, K. R. (1951). *Amer. J. Ophthal.*, **34**, 543.
HINGSON, R. A., STOELTING, V. K., GRAF, J. P., and VIEIRA, Z. (1949). *Curr. Res. Anesth.*, **28**, 130.
KIRBY, D. B. (1950). *Arch. Ophthal., Chicago*, **43**, 678.
ROCHE, J. R. (1950). *Amer. J. Ophthal.*, **33**, 91.

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PENETRATING CORNEAL GRAFT*

ORIENTATION OF THE INITIAL PENETRATION OF THE TREPHINE INTO THE HOST CORNEA

BY

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DURING the operation of perforating graft of the cornea, the trephine in the great majority of cases enters the anterior chamber in only a portion of its circumference, the remaining circumference of the graft being completed with scissors. The author has noticed, both in operations performed personally and in those performed by others, that the portion of the circumference of the trephine which first enters the anterior chamber is usually that nearest to the wrist of the operating hand, despite the customary effort of making an even trephine cut. Since this was first noted, particular attention has been directed to it, and it has been found that in all of six perforating graft operations performed during a period of 3 weeks the trephine entered the anterior chamber on the wrist side.

To confirm this observation, sixteen enucleated eyes were trephined with the same care as would be used in the operating theatre for the recipient eye. That is, the trephine cut was stopped as soon as it was clear that the anterior chamber had been entered. In five cases the anterior chamber was entered practically simultaneously in the entire circumference of the trephine cut, and in the remaining eleven cases, the anterior chamber was entered nine times on the wrist side, and twice on the other side. The fairly large proportion of cases (six out of sixteen) in which the whole circumference of the trephine reached the anterior chamber simultaneously was probably due to the relative confidence of the laboratory as compared with the operating theatre.

It would appear that, so far as the author is concerned, there is a tendency to tilt the trephine in the direction of the wrist of the hand holding it, despite the effort to keep the instrument vertical.

Application

It was found that clinically, advantage might be taken of this circumstance in the following conditions:

(1) *In cases in which a perforating graft operation is performed despite the presence of a small anterior synechia, the intention being to separate the synechia during the operation.*

* Received for publication April 29, 1953.

The synechia may have remained after a preliminary synechiotomy operation, and not be large enough to demand a further preliminary synechiotomy. In these cases it is easier to separate the synechia if the initial entry of the trephine into the anterior chamber is made in the sector of the cornea in which the synechia is situated. The reasons for this are as follows:

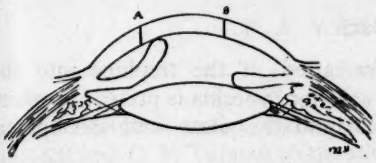

FIG. 1.—A and B represent the limits of the portion of the host cornea which is to be removed. A is situated over the portion of the iris where there is a small anterior synechia. It is advisable that, if all the graft is not cut with the trephine simultaneously, the anterior chamber be entered at A rather than at B. This permits easier and safer separation of the anterior synechia. The trephine is therefore held by the author so that his wrist is directed towards A.

(*a*) The synechia should be separated before the scissor portion of the circumference is cut, thereby facilitating the latter manoeuvre. This can be done if the synechia is in the portion of the cornea where the initial entrance into the anterior chamber is made.

(*b*) It is better to approach a synechia from the limbal side rather than from the pupil side. The former procedure permits stretching the synechia, and at the same time the dividing instrument, scissor or spatula, is protected from the lens by the body of the iris (Fig. 1).

Therefore, the trephine should be held so that the surgeon's wrist is at that side of the trephine which is in the same meridian as the anterior synechia.

(2) *In cases in which the trephine cut traverses opaque and transparent portions of the cornea.*

It is advisable to have the trephine portion of the cut in the opaque area and the scissor portion in the transparent area. The reasons are these:

(*a*) The trephine portion of the cut heals quicker than the scissor portion and should therefore be sited in the opaque portion of the cornea which heals less quickly than the transparent portion.

(*b*) The scissor cut can be made more accurately in transparent cornea than in opaque cornea.

Therefore, if the cut must traverse opaque and transparent portions of a recipient cornea, the trephine should be held so that the surgeon's wrist is at that side of the trephine which lies over the opaque portion of the cornea (Fig. 2).

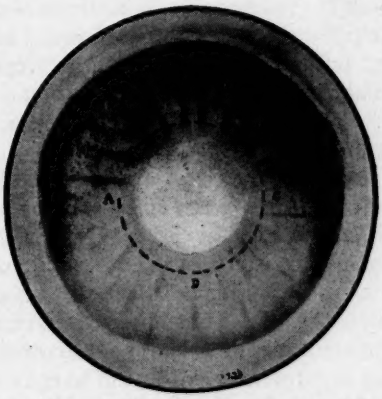

FIG. 2.—ABCD is the circumference of the portion of the host cornea which is to be removed. The portion ABC traverses relatively clear cornea, the portion ADC lies in dense opacity. It is advisable that if any portion must be cut with scissors it should be that corresponding to ABC. The trephine is, therefore, held by the author so that his wrist is directed towards 6 o'clock.

These small practical points are put forward because success or failure in graft operations rests in most cases upon scrupulous attention to detail. It is appreciated that the orientation of the initial penetration into the

cornea according to the position of the surgeon's wrist may be peculiar to only a few. It is, however, suggested that each surgeon should examine his own proclivity in this direction, so that the tendency, if found, may be exploited clinically as described above.

Summary

(1) The meridian of the initial penetration of the trephine into the cornea is of some importance where an anterior synechia is present or where the circumference of the cut traverses both the clear and the opaque regions of the cornea.

(2) It is shown in the author's own case that the position of the wrist of the hand holding the trephine determines the meridian of the initial penetration of the trephine into the recipient cornea.

(3) It is suggested that others may find a personal tendency for the trephine to enter the anterior chamber in a meridian determined by the position of the hand holding the instrument.

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DETECTION OF GLAUCOMA IN GENERAL PRACTICE*

BY

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London

AT the International Congress in 1950, Conrad Berens read a paper by himself and C. P. Tolman to the International Association for Prevention of Blindness, on "The Prevention of Blindness from Glaucoma". In the course of this he suggested that the most effective approach to the problem would be through the medical profession rather than by propaganda, a view with which I think we should all agree. The need for a crusade against glaucoma is shown by some figures quoted in the paper: the Philadelphia Committee for the Prevention of Blindness found that, of 10,500 adult workers over 40 years of age, 280 (2·7 per cent.) had undiagnosed ocular hypertension and that only four out of the whole group knew that they had glaucoma.

It seems that in some respects to take the estimation of intra-ocular pressure as the criterion for presumptive diagnosis of glaucoma is open to criticism. First, the application of a tonometer demands a certain amount of skill and practice. It is also time-consuming, a factor of some importance to the present-day general practitioner. Secondly, owing to the well-known diurnal variations of intra-ocular pressure, quite a number of cases of mild chronic glaucoma may have a normal tension at the time of examination. This fact is recognised by ophthalmologists and it has become the custom with many when encountering a case showing signs of glaucoma with a normal tonometric reading, to admit him or her as an in-patient for periodic estimations every 2 or 4 hours over a period of 1 or 2 days. Thirdly, certain people seem to have an abnormally high tension, even up to 40 mm. Hg, without any deleterious effect on the eyes over a period of years.

There would seem therefore to be a need for some other test which would be simple and inexpensive to apply, as well as reliable. The detection of an arcuate scotoma seems to be the most important single observation to be made in the diagnosis of early glaucoma, especially as such a scotoma can sometimes be present in cases showing a normal peripheral field. Admittedly, such a scotoma is not irrefutable evidence of the presence of glaucoma and I have twice seen one produced by blockage of one of the small arteries going to the macula, but such cases are rare and in any event, if picked up during the course of general practice, should be sent on to the ophthalmologist. Very occasionally, one comes across a case in which there is ocular hypertension with loss of nasal field but no arcuate scotoma, but such cases are

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very rare and I can remember seeing only one in the course of some 30 years' work. In this case, the lamina cribrosa must have been pretty tough, because it showed no trace of cupping, in spite of a tension of +2 to fingers and the loss of a quadrant in the upper nasal field. I do not wish, however, to enter into a discussion about the mechanism of production of an arcuate scotoma except to say that a pre-requisite is some degree of cupping of the disc, even though this may seem not to exceed physiological limits.

If, then, it is accepted that detection of an arcuate scotoma (or only the beginnings of one as shown by an area of defective vision near the fixation point and usually in the vertical meridian) is the most useful single test for glaucoma, how can one best set about detecting it, in the circumstances of general practice? Some form of Bjerrum screen would be the ideal, but this is neither practicable nor necessary, because all the examiner requires at this stage is to establish the presence or absence of a scotoma; more detailed examination will be carried out later by an ophthalmologist.

The schoolboy trick of a cross and a dot on the back of an envelope, which shows the existence of the blind spot, will be remembered by many. The test I had made is derived from this and consists essentially of a white bar about 15 cm. long, with a black dot, 3 mm. in diameter, at one end and a cross on a movable cursor (see Figure). At the end of the bar opposite to the dot is attached a cord 33 cm. long, knotted at the end, with a small notch above the attachment. On the back of the bar are two transverse lines marked 1/6 and 1/3 m.

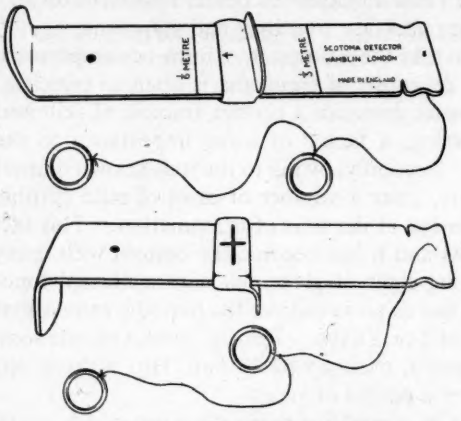

FIGURE.—Scotoma Detector.
(*a*) Surface which faces examiner.
(*b*) Surface facing patient.

When the instrument is to be used, say on the patient's right eye, he is instructed to cover the left eye and the bar is held in front of him at a distance of 1/3 m.—as measured by the attached cord. Since the centre of the blind spot is 15° temporally from the fixation point and some 7° below it, the bar is inclined at 7° below the horizontal with the dot on the temporal side and the cursor as far from the dot as it will go. The patient is instructed to look at the centre of the cross and to notice that, although not looking at it, he is conscious of the dot. The cross is now slid slowly along and the patient is asked to say when the dot disappears and when it comes into view again. Contrary to what happens on the Bjerrum screen, success is usually achieved

at the first attempt, perhaps because the examiner is standing opposite the patient and can watch the movement of the eye (and also perhaps for another reason which I shall mention later). The existence of a blind spot being established, the bar is now held vertically and the manoeuvre repeated, first with the dot above and then with it below. If there is no scotoma, the dot does not disappear in either position, but if there is one it never fails to do so, at any rate in my experience.

In April, 1952, I saw a patient aged 49 with a large cup in his right disc and a typical scotoma below the fixation point. The scotoma showed up well on the instrument I have just been describing, the dot disappearing when it was below the cross but not when above. He came back 2 months later when I was at first disappointed to find that even with repeated trials the dot failed to disappear, but, on going over his central field on the Bjerrum screen to map out the scotoma again, I was surprised to find that as a result of pilocarpine drops it had disappeared. It looks therefore as though the instrument may be reliable, though I have not used it on enough cases to be dogmatic on this point. If desired, the test may be carried out at 1/6 m. by doubling the string and catching the knot in the nick, but this is seldom necessary. The lines on the back indicate the positions of the cursor at which the dot should disappear at 1/3 and 1/6 m. respectively, when it occupies the centre of the normal blind spot.

In presbyopes—and most of the potentially glaucomatous are in this category—it is as well for the patient to wear his reading correction though it is not usually essential. If bifocals are worn, one should make sure that the dot and cross are being viewed through the reading portion, otherwise the dot may seem to disappear when its image crosses the dividing line between the two parts of the spectacle lens. This is particularly liable to happen in the vertical meridian when the dot is above the cross and the patient is wearing bifocals which have a jump.

My experience with this instrument in which, to coin an Irish bull, the patient is fixing a moving object, made me wonder whether the same principle might not be applied to screen examination. Physiologically it is more natural for the eye to keep moving. Up to date, I have tried this only a few times and it certainly works, but I have not yet devised the best arrangement for doing it. I am waiting for a case of vascular hemianopia with sparing of the macula. Among the various theories accounting for this condition is that it is due to imperfect fixation, and if this is so, the sparing might not be so evident when the patient was looking at a moving object. In carrying out this method, the patient is directed to look at the target on the end of the holder which the examiner moves in the usual way, and to say when, what was formerly the fixation point, appears or disappears. A complication occurs in recording the scotoma or loss of field, because this has to be done so to speak looking-glass and upside down. This is not difficult when using

pins on the screen, however, because one puts them in at the diametrically opposite point to that occupied by the disc on the holder.

This however is not my main subject, at any rate at present, because what I wanted to describe was a quick and effective way by which the general practitioner could detect chronic glaucoma. The method is also useful for the ophthalmologist, particularly in those cases where there is doubtful cupping and one is pressed for time, as so often happens in hospital work.

I should like to thank the late Mr. Theodore Hamblin for his kind co-operation in producing this instrument, and his drawing department for preparing the Figure and supplying the block.

REFERENCE

BERENS, C., and TOLMAN, C. P. (1951). "XVI Concilium ophthalmologicum, 1950, Britannia Acta", vol. 2, p. 1499.

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A MEDICAL FISH STORY*

[THE claim by Mr. R. F. Shropshire to cure cataract with injections of fish-lens protein has drawn some attention in Great Britain, which has been fostered by misleading reports in the lay press. The following extracts reprinted from the *Journal of the American Medical Association* may interest our readers. Ed.]

EDITORIAL

A report of the Committee on Ophthalmology of the National Research Council, Division of Medical Sciences, on the fish-lens protein treatment for cataract appears elsewhere in this issue. As is mentioned in the report, an investigation was made because of widespread public interest in what appeared to be an escape from necessary surgery in the treatment of cataract. Such interest resulted from newspaper stories, which, unfortunately, aroused false hopes in many persons. These stories were based on a report which appeared in *Science*, a reputable scientific weekly, in September, 1952 (Shropshire, Ginsberg, and Jacobi, 1952). Since that time two or three physicians in the New York metropolitan area have treated many patients. The *Journal of the American Medical Association* has published an earlier warning (Posner, 1953) of possible untoward results of this injection therapy.

The principal author of the *Science* report is, according to most recent authentic information, in prison in Florida, awaiting a hearing on the matter of revocation of his parole for alleged violation of the terms thereof. Presumably, these alleged infractions did not involve the matter of participation in the treatment of persons with cataracts with what may well have been contaminated fish-lens protein material. Such activity would, however, appear to be the most serious aspect to be considered. His medical confreres should consider seriously these effects.

MR. R. R. SHROPSHIRE'S NONSURGICAL TREATMENT OF CATARACT

Report by the Committee on Ophthalmology of the Division of Medical Sciences of the National Research Council of the U.S.A.

On September 12, 1952, there appeared in *Science* an article reporting beneficial effects from the nonsurgical treatment of cataract with injections of fish-lens protein (Shropshire, Ginsberg, and Jacobi, 1952). Because of the widespread public interest that it aroused and because of the inadequacy of the evidence presented, the Council of the American Academy of Ophthalmology and Otolaryngology petitioned the National Research Council to investigate the authors' claims. An investigation was made by the National Research Council Committee on Ophthalmology, whose findings and recommendation form the basis for this report.

The hypothesis that lens antigens might be useful in the treatment of cataract is not new. Römer (1908) reported success in treating cortical cataract with tablets of mammalian lens protein. Davis (1923, 1925), in the U.S.A., attempted active immunization with bovine lens material. His favourable reports led to a number of other investigations (Berens and others, 1927; Ellis, 1928; Kirby

*Reprinted from the *Journal of The American Medical Association* (1953), 152, June 20, 717, and 707, by permission of the Publishers.

and Giles, 1930; Biffis and Quaglio, 1933; Selinger, 1935). These, however, failed to confirm his findings, and the proposed therapy lapsed into obscurity.

The use of fish-lens protein was attempted by Lewis (1933), with whom its present proponent, Mr. R. F. Shropshire, was then associated. Again favourable results were claimed, but the ophthalmological details presented were unconvincing, and the report aroused little interest on the part of the profession.

Mr. Shropshire's interest, however, continued, and in 1937 he published two papers on the subject (Shropshire, 1937 a,b). In addition to reviewing Lewis's work, he cited Hektoen and Schulhof (1924) as evidence that the lens proteins of fish are immunologically different from those of mammals. In fact, these authors had specifically stated that fish lens contains antigens that interact with mammalian lens, in addition to others that are species specific. Shropshire also reported chemical differences between piscine and mammalian lenses; being able to account for only a part of the sulphur content of fish lenses, he postulated the existence of a previously undescribed sulphurbearing amino acid of therapeutic value. Unfortunately his analytical methods were not suitable for the detection of either cystine or methionine; the latter alone accounts for about half of the sulphur present, and cysteine and cystine almost completely account for the rest (Dische and Zil, 1951).

The chemical argument is extended in the recent paper of Shropshire and others (1952), which reports that differences were found between the electrophoretic and ultracentrifugal patterns of mammalian and piscine lens protein. According to the detailed report furnished to the Committee on Ophthalmology, these studies were performed by Dr. Kurt G. Stern with human and piscine lenses. Since the patterns of bovine and human lens proteins are also very different from one another, the observations of Stern do not support Shropshire's claim that fish lens has distinctive qualities of possible therapeutic value. In any case no deductions as to anti-genic behaviour can be made legitimately from physicochemical measurements of the type described.

The article in *Science* is chiefly notable for its reports of the successful treatment of cataract in rats and humans with injections of fish-lens protein. On investigation, it developed that cataracts had been induced in the rats by feeding them galactose. Since such cataracts appear superficially to clear when the administration of galactose is stopped regardless of treatment, these observations do not provide convincing evidence in favour of the fish-lens therapy.

The most impressive claim was that of improved visual acuity in the patients treated by Shropshire's co-authors, Drs. Ginsberg and Jacobi. The article referred to an initial group of fourteen patients, described in general terms, and an additional twelve whose acuities before and after treatment were given in a Table. In order to provide an independent evaluation of these claims, arrangements were made for a subcommittee of the Committee on Ophthalmology to examine a group of patients selected by the proponents of the therapy. Eleven patients were examined, all of whom were enthusiastic about the benefits that they had obtained. The findings were compared with those recorded when the treatment was begun. In six patients the visual acuity was less than before treatment, and the cataracts appeared to have progressed steadily in the usual fashion. Two others showed the little or no change. The remaining three showed slight or questionable improvement; of these two had vitreous opacities, and their subjective reports clearly supported the conclusion that the improvement had been due to shifting these opacities out of the

line of vision. In only one patient did the data appear to suggest an actual improvement; since, however, neither Shropshire not his collaborators were ophthalmologists their original estimate in this case may have been in error.

The subjective improvement, in most cases, was in near vision; the obvious explanation of this is the development of functional myopia in a progressing cataract. Two patients, as mentioned, were pleased because their vitreous opacities seldom bothered them, and another because his sensitivity to light and multiple vision when looking at lights had disappeared. With the possible exception of one patient, therefore, there was no evidence that the normal course of the cataracts had been affected by the treatment.

A later report received by the Committee on Ophthalmology described the results of treatment administered independently by an ophthalmologist on the staff of a recognized medical school, using fish-lens protein supplied by Mr. Shropshire. The cases were unselected, and included fourteen eyes with cataracts in nine patients. No objective change in the cataracts could be discovered; in four cases vision as measured by the test chart was slightly improved, while in two it was worse. Seven patients reported subjective improvement which the physician considered to be psychological; one felt that she was worse.

Further evidence indicates that treatment with foreign lens proteins is not merely ineffective but also hazardous to the patient. Posner (1953) called attention to serious reactions, leading in one case to total blindness, in patients sensitized to their own lens protein by injections of both beef and fish-lens extracts; he warned ophthalmologists of the dangers that may arise when such patients come to operation. This was corroborated by a member of the Committee, who referred to the unfortunate post-operative histories of patients treated unsuccessfully with beef-lens protein. It should further be noted that of twelve sample bottles of the fish-lens preparation furnished to the Ocular Research Unit of the Walter Reed Army Hospital by the Cataract Institute, ten were contaminated with pathogenic organisms.

The Committee also inquired into the backgrounds and qualifications of the proponents, to determine how much credence might be given to their reports. No evidence was found that Mr. Shropshire had had any formal scientific training; claims that he was a graduate physician and had conducted research in ophthalmological chemistry at two universities were not substantiated by the institutions concerned. He has, however, tried his hand at a variety of scientific undertakings. As noted above, he was an assistant to the late Dr. F. Park Lewis, an ophthalmologist, about 1933, at which time he published a paper on the eye of the trout. Subsequent activities included two appointments as a laboratory technician in pathology, from which he was dismissed for lack of competence and for unreliability due to drug addiction, and brief experience in research in underwater sound. In 1944 he posed as a pathologist in Florida, and, after pleading guilty on three counts of forging prescriptions for narcotics, was sentenced to serve five years on the first count and five on the second, the sentences to run consecutively. About one year later he was paroled. This parole was revoked in 1948; excessive use of alcoholic drinks, suspected use of narcotic drugs, and issuing of bad cheques were given as the reasons. It was after a second parole in 1949 that he engaged, with private sponsorship, in his recent studies on experimental cataract in the rat.

In a chance meeting with Shropshire, a New York business man, Mr. Saul Gaynes,

became interested in the financial possibilities of the fish-lens preparation. Clinical trials were begun by his brother, Dr. Ginsberg, a general practitioner, and Dr. Jacobi, an internist. Encouraged by the early reports, Gaynes and Shropshire incorporated the Kortright Industries to manufacture and sell the preparation. With three others they also established the Cataract Institute, as a nonprofit corporation to conduct research on the pathogenesis and therapy of cataract, and Shropshire was given a five year contract as consultant. A third physician later joined the group, Dr. Jacob Weynert, an orthopaedist. For a time patients were examined by opticians in the employ of a New York optical company.

In summary, the Committee found nothing in the theoretical background or in the experimental and clinical results of this therapy to recommend it. It did, however, find evidence that the treatment might seriously interfere with the subsequent surgical removal of the cataracts that it had failed to cure. In view of these facts, the Committee adopted the following statement of its conclusions:

Because of the total lack of evidence that the lens antigen treatment of cataract described by Mr. R. F. Shropshire (*Science*, September 12, 1952) has any efficacy, because adequate evidence is now available to the Committee that it is, in fact, without demonstrable efficacy, and because treatments of this type have been thoroughly investigated in the past and proved not only invalid but potentially dangerous to the patient, this Committee does not recommend further investigation of this treatment by any agency.

REFERENCES

BERENS, C., and others. (1927). *Atlant. med. J.*, **30**, 547.
BIFFIS, A., and QUAGLIO, C. (1933). *Ann. Ottal.*, **61**, 641.
DAVIS, A. E. (1923). *Amer. J. Ophthal.*, **6**, 295.
——— (1925). *Arch. Ophthal., Chicago*, **54**, 172.
DISCHE, Z., and Zil, H. (1951). *Amer. J. Ophthal.*, **34**, May (Part 2), 104.
ELLIS, Z. H. (1928). *Arch. Ophthal., Chicago*, **57**, 46.
HEKTOEN, L., and SCHULHOF, K. (1924). *J. infect. Dis.*, **34**, 433.
KIRBY, D. B., and GILES, N. W. (1930). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **35**, 309.
LEWIS, F. P. (1933). *In* " XIV Concilium ophtalmologicum 1933, Hispania", vol. 1, p. 209. Madrid.
POSNER, A. (1953). *J. Amer. med. Ass.*, **151**, 317.
RÖMER, P. (1908). *Ber. dtsch. ophthal. Ges.*, **35**, 195.
SELINGER, E. (1935). *Arch. Ophthal., Chicago*, **14**, 244.
SHROPSHIRE, R. F. (1937a). *Ibid.*, **17**, 505.
——— (1937b). *Ibid.*, **17**, 508.
——— GINSBERG, J. R., and JACOBI, M. (1952). *Science*, **116**, 276.

Brit. J. Ophthal. (1953) **37**, 573.

BOOK REVIEWS

Physiology of the Eye. Vol. II. Vision. By ARTHUR LINKSZ. 1952. Pp. 869, 248 figs, bibl. Gruner and Stratton, New York. (£7 12*s.*; $19).

Those who have had the experience of reading the first volume of Linksz's " Physiology of the Eye " will be delighted to welcome the appearance of the second. The first volume dealt with optics; the second, which deals with the physiology of vision, is equally delightful to read, equally original in its presentation, and equally provocative in its message. The cultural background of the author is everywhere apparent—Europe, Prague, and Hering—but, although bias may occasionally exist, common sense is everywhere, tradition for its own sake is thrown overboard, and originality abounds.

The first section (eight chapters) which comprises a general analysis of sensation, is largely occupied by a discussion of the sensations of light and colour. The second section deals with the appreciation of pattern and detail, and problems of visual acuity. Linksz does not give the " form sense " the status of a specific " sense "—and his reasons are good. The third section discusses the perception of spatial relationships, including such problems as the geometry of the horopter, true and anomalous correspondences, aniseikonia, and so on. The last section deals in considerable detail with the oculo-rotatory reflexes and their relation to vision. This is a book which ought to be read—and read slowly—by everyone interested in the complex and fascinating problems of the physiology and psychology of vision.

Cortisone and ACTH in Clinical Practice. Edited by W. S. C. COPEMAN. 1953. Butterworth, London. Pp. 255, 29 figs, bibl. (25*s.*)

This book gives a concise survey of the present position of cortisone and ACTH therapy. Each section has been written by a specialist in one particular branch of the subject, and the references at the end of each provide adequate opportunity for further reading and form a representative selection from the current literature.

The editor has written the section on the rheumatic and collagen diseases himself, and combines a review of modern trends in treatment with an account of his own wide clinical and research experience in this field. The cautionary note on which the section concludes indicates the difficulties encountered in the treatment of rheumatoid arthritis, and the disappointments which sometimes follow the withdrawal of the hormone.

F. Dudley Hart, in the section on endocrine disorder, pays particular attention to the use of cortisone in Addison's disease and Simmonds's disease, in which conditions it constitutes orthodox therapy. The results in thyrotoxicosis and thyrotropic exophthalmic ophthalmoplegia are too variable for significant claims to be established.

Sections in which respiratory, allergic, and skin diseases, and disorders of the hæmopoietic system, are fully discussed in relation to cortisone and ACTH maintain the emphasis on the value of these hormones and their limitations.

Sorsby and Savory, in the section on ocular diseases, quote experimental investigations into the concentration of cortisone in the aqueous and vitreous after local and systemic administration, and after the systemic administration of ACTH. In considering the clinical aspects of treatment with cortisone and ACTH, they give a detailed account of the methods of local and systemic administration, and a very guarded report of the value of this treatment in various ocular diseases. Although there are many conditions of the eye in which cortisone is of no assistance, and a few in which it is actually dangerous, increasing experience of its use indicates that the views of these authors are to some extent unduly pessimistic.

NOTES

British Medical Association

Annual Congress, 1953

At the 121st Annual Congress of the B.M.A., held in Cardiff, J. W. Tudor Thomas was installed as President on July 13, 1953. It will be recalled that only five ophthalmologists—Reeve (*Toronto*), Snell (*Sheffield*), Harvey Smith (*Winnipeg*), Sir James Barrett (*Melbourne*), and Sichel (*Capetown*)—have previously been honoured with the presidency of the Association, and Tudor Thomas's year falls exactly 100 years after the first occasion when the Annual Meeting was held in Wales (Swansea, 1853). Charles Hastings, the founder of the Association, once enjoined his colleagues to serve "with head, and heart, and hand"; and this phrase was a happy choice for the title of Mr. Tudor Thomas's presidential address, which ranged widely over the field of general medicine, as well as dealing with advances in ophthalmology.

The President's Reception was held at the National Museum of Wales. On this occasion, and in the course of their numerous other engagements throughout the Congress, Mr. and *Mrs. Tudor Thomas communicated an atmosphere of informality and individual welcome.* He presided with a distinction which was rendered all the more effective by the support of his charming lady.

Mr. Tudor Thomas also found time to attend part of the meeting of the Section of Ophthalmology, where two subjects were discussed. Mr. G. I. Scott (*Edinburgh*) and Dr. Leonard Howells (*Cardiff*) gave opening papers on "The Ocular Complications of Diabetes", and were followed by Mr. A. B. Nutt (*Sheffield*). The other subject, "The Scope of Corneal Graft Surgery", was opened by Mr. B. W. Rycroft (*London*), and subsequent speakers were Mr. E. C. Zorab (*Southampton*), Mr. J. Ayoub (*London*), and Mr. A. G. Leigh (*London*).

The officers of the Section were:

PRESIDENT: J. H. Doggart (*London*).
VICE-PRESIDENTS: Rupert J. Parry (*Cardiff*), Roy Thomas (*Swansea*), Eugene Wolff (*London*);
HONORARY SECRETARIES: Bernard Gluck (*Cardiff*), A. J. B. GOLDSMITH (*London*).

XVII International Congress of Ophthalmology, 1954

Readers of the Journal will recall from the minutes of the International Council published in our August issue that this body recommended that the XVII International Congress should be extended in scope and time, the suggestion being that it should open in Montreal on September 10, 1954, and that Congressists should travel from that city on September 12 to New York, where meetings will be continued until September 17. The following week the Annual meeting of the American Academy of Ophthalmology and Otolaryngology will also be held in New York. Final particulars of these arrangements will be published in the immediate future by the Executive Committee of the Congress in the U.S.A.

Finance.—In order to help those who would find it difficult to attend the Congress for financial reasons, two potential sources of money are available:

(a) The Faculty of Ophthalmologists has set aside a fund in sterling for financial assistance in this respect. A sub-committee has been set up to recommend to the Faculty the allocation of this money; those wishing to make application should do so to Mr. Frank Law at 36, Devonshire Place, London, S.W.1. Such applicants should be of British nationality.

(*b*) The International Council of Ophthalmology has allocated the surplus funds available from the XVI International Congress (*London, 1952*) to the same object. The committee in charge of the allocation of these funds is composed of the officers of the Council, and application should be made to Dr. Edward Hartmann at 2, Avenue Ingres, Paris, XVIe. Applicants for a grant from this source may be of any nationality.

In each case grants will be given to those who propose to make a substantial contribution to the proceedings of the Congress, but who would otherwise find it difficult to meet the whole of the necessary financial outlay of travel to North America. Applications should be made before December 31, 1953.

Travel.—The task of making provisional travel arrangements in connection with the *XVII International Congress of Ophthalmology* has been entrusted by the Ophthalmological Society of the United Kingdom and the Faculty of Ophthalmologists to Sir *Stewart Duke-Elder* and Mr. Frank Law.

Special arrangements have been made by the Cunard Line for the *Samaria* (20,000 tons) to sail from Southampton and *Le Havre on September 1, 1954, so that* delegates to the Congress may arrive directly in Canada on September 9, in good time for the opening meeting. *It is imperative that intending delegates should* communicate immediately with the Cunard Steamship Company Ltd. (Mr. H. S. Taylor), Cunard Bldg., 15, Lower *Regent Street, London, S.W.1., stating* whether tourist or first class berths are required.

Single fares by sea from Southampton: Tourist Class, £55 10s; First Class, £83 upwards; from Le Havre: *Tourist Class, $160; First Class, $240.50 upwards.*

Delegates who prefer to arrive in Montreal a few days before the Congress begins will have a choice of suitable sailings with either the Cunard or *the Canadian Pacific Line* (e.g., *Empress of France*, arriving Montreal September 3).

Eastbound sailings from New York after the Congress are scheduled as *follows:*

September 17 *Media* (New York to Liverpool).
September 18 *Mauretania* (New York to Southampton *via Cobh [Queenstown]* and Le Havre).
September 22 Queen Mary (New York to Southampton *via* Cherbourg).
September 29 *Queen Elizabeth* (New York to Southampton *via* Cherbourg).

Ocean fares for the homeward passage will be subject to the lower off-season rates.

The officially appointed agents in the U.S.A. are the American Express Co. Inc. Messrs Thomas Cook and Son Ltd., are also acting as agents in the United Kingdom. Detailed information regarding air and sea passages, and also air and rail fares between Montreal and New York will be available next month.

HONOURS

MR. J. H. DOGGART, F.R.C.S., has been elected to the Court of Examiners of the Royal College of Surgeons of England as an examiner in the final F.R.C.S. with Ophthalmology.

MR. A. B. NUTT, F.R.C.S., has been appointed to a Hunterian Professorship at the Royal College of Surgeons of England.

ANNOTATION

MANY years ago I obtained a dozen pig's eyes for the purpose of trying different techniques in cataract extraction. Some of the eyes were left over, and my elder son, then aged about 10, wanted to know what they were for. I showed him how to remove a lens and he asked if he could try and succeeded at his first shot. Then he asked me, " Do you get a hundred guineas for doing that on a patient ? ", to which I replied, " Occasionally ". He thought that this would be a good way of earning a living but I thought it would be as well to let him see another side of our specialty. So a few weeks later on a wet Sunday, when the two boys having nothing better to do were being entertained by me in the consulting room, I made the elder work out his younger brother's refraction. It took some time to do and at the end I was asked, " Do you have to do this on every patient? ", to which I replied that I had to, on practically all. From that day forward ophthalmology as a future career became less attractive.

This experience brought home to me how deadly dull a whole day spent in refraction work could be, were it not for the endless variety in the characters of those who owned the eyes one was testing and in their responses to the tests one used. An interesting distinction between children and adults is shown in their replies to the familiar question, " Can you see the bottom line ? " A child will nearly always say " Yes " or " No " as the case may be, whereas an adult prefers to read the letters aloud if he can see them. The child presumably expects to be believed or has the common sense not to bother himself to read out a long line of letters if he can avoid it, whereas the adult, having been in contact with the world for considerably longer, knows he must prove his statement.

Children's clear-cut logic can be a little upsetting at times. I remember once testing a small boy with the Maddox rod and explaining to him that he would see a red line and a light. I switched the light on and asked if he could see the red line, to which he replied with an uncompromising " No ". I then covered the eye which was viewing the light and asked him if he could see the red line, but he still said he could not, so finally I asked him what he could see and he replied, " A red line ". I told him that this was what I had been asking him about, and he replied " Oh no, you said I'd see a red *lion* ".

The story of the small boy who refused to read the letters because they did not spell anything is too well known to need recital in detail, but occasionally the same thing happens in adults, only in their case the refusal is because the letters, not being clearly seen, appear to spell a word which from motives of decency they refuse to pronounce. One such line occurs as 6/12 in a well-known set of test types.

Annotations in the past have usually carried a moral, but it is difficult to find one here unless it be that even in refraction we can at times " Behold the bright original appear ".

CORRIGENDA

The caption to Fig. 2 in the article entitled " Variant of the Lancaster Diplopia Test " by John Foster which appeared in the *British Journal of Ophthalmology*, 1953, **37**, 378, should read " The position of the strip of light projected by the red torch when held by the patient is marked by the *red* line, and that of the green torch when held by the patient by the *green* line ".

The antibiotic " Aerosporin " (see the footnote to an article entitled " *Ps. Pyocyaneus* Eye Infection " by Marguerite Macdonald, *British Journal of Ophthalmology*, 1953, **37**, 371) is manufactured by Messrs Burroughs Wellcome and Co., England.